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(54) **METHOD AND IMPLANTABLE SYSTEM FOR BLOOD-GLUCOSE CONCENTRATION MONITORING USING PARALLEL METHODOLOGIES**

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A61B 5/04 (2006.01)
A61B 5/1455 (2006.01)
A61B 5/1459 (2006.01)

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

In an implantable medical device for monitoring glucose concentration in the blood, a blood-glucose concentration analysis is performed using correlations of blood-glucose concentration with measures of metabolic oxygen consumption including oxymetric, and/or temperature. Analysis of electrocardiographic data is used in a parallel method to detect and/or confirm the onset and/or existence and/or extent of hypoglycemia and/or hyperglycemia. Blood-glucose concentration calculation is enhanced by using the combination of the oxygen metabolism analysis and electrocardiographic analysis.

10 Claims, 17 Drawing Sheets

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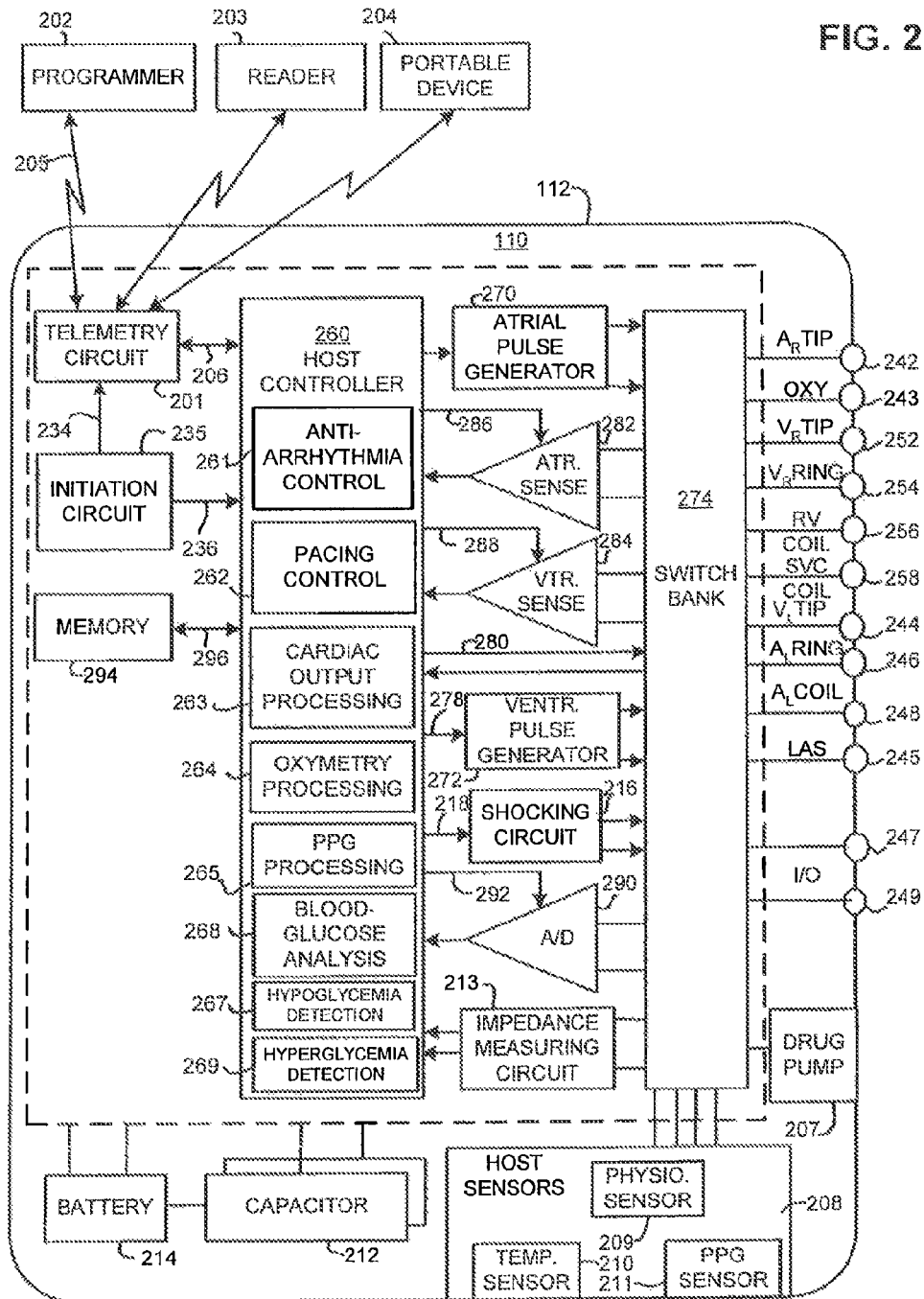


FIG. 3

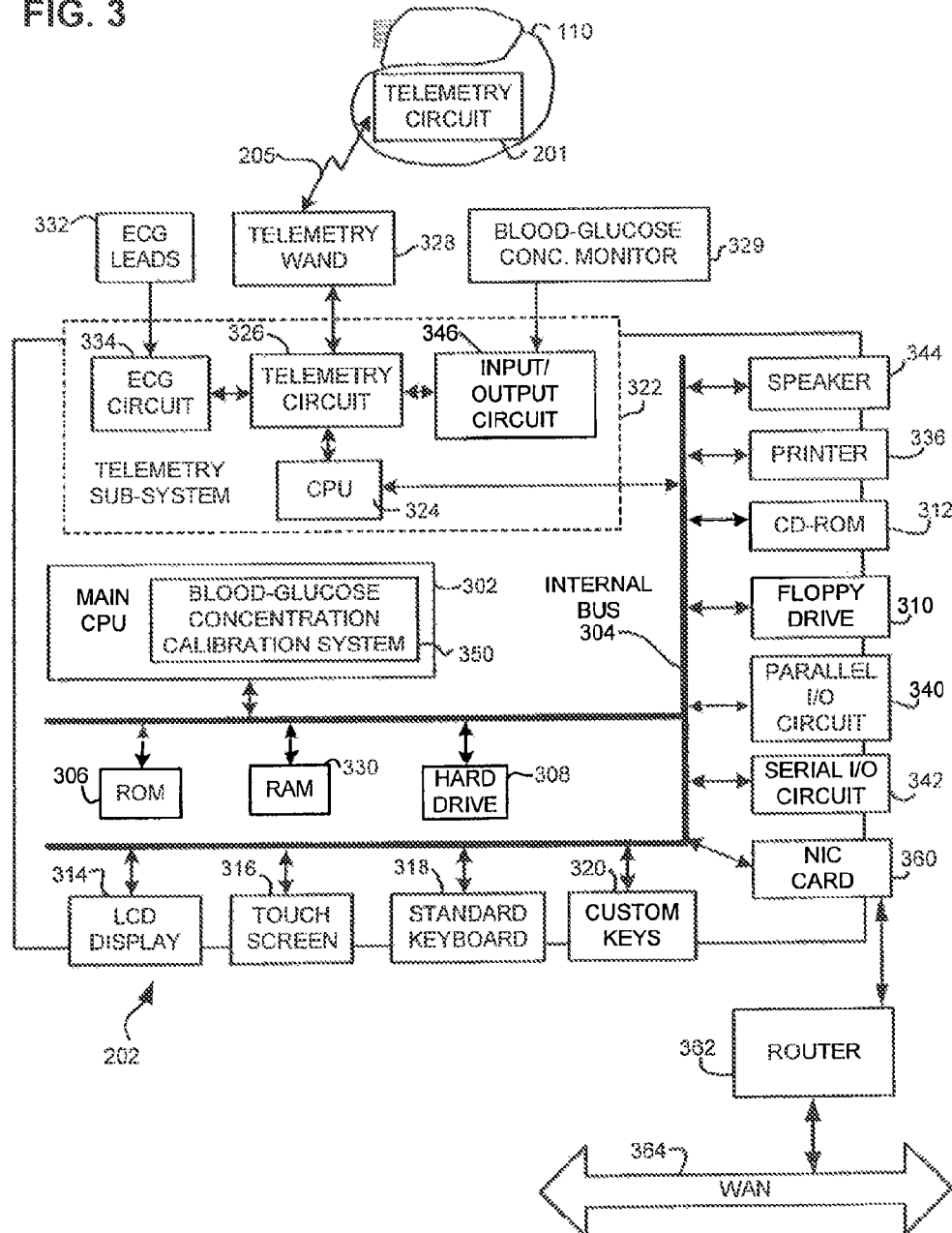


FIG. 4

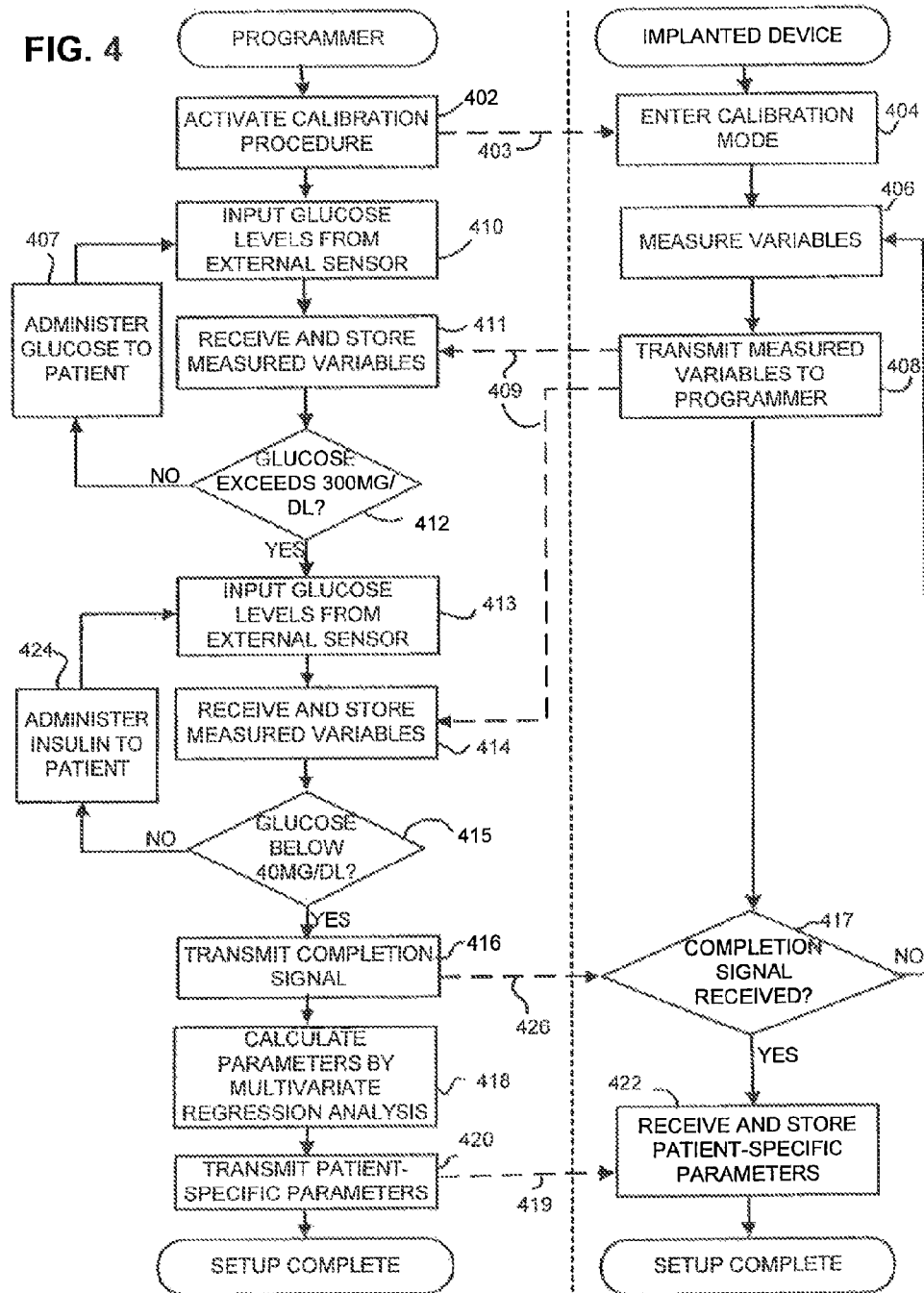


FIG. 5A

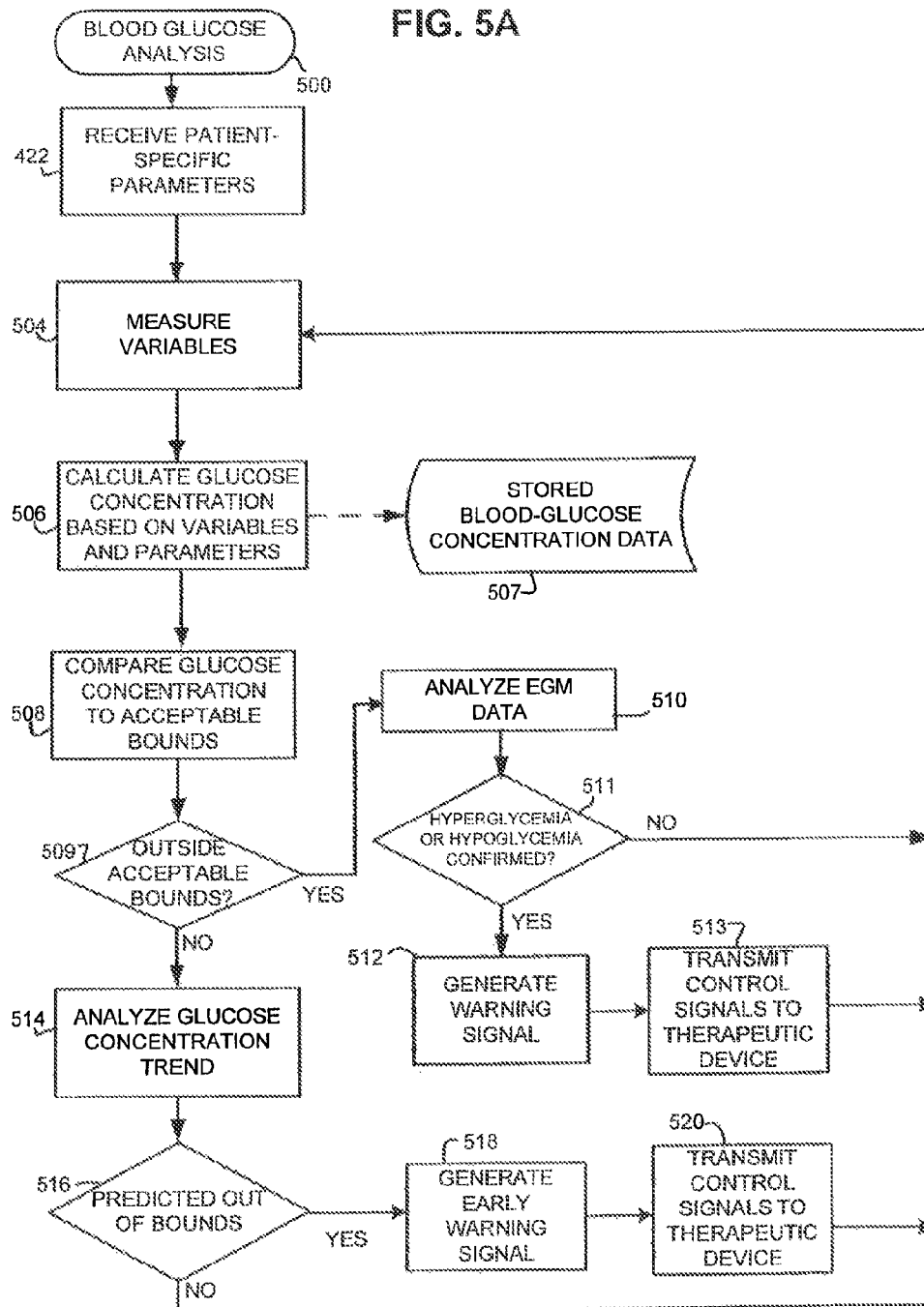
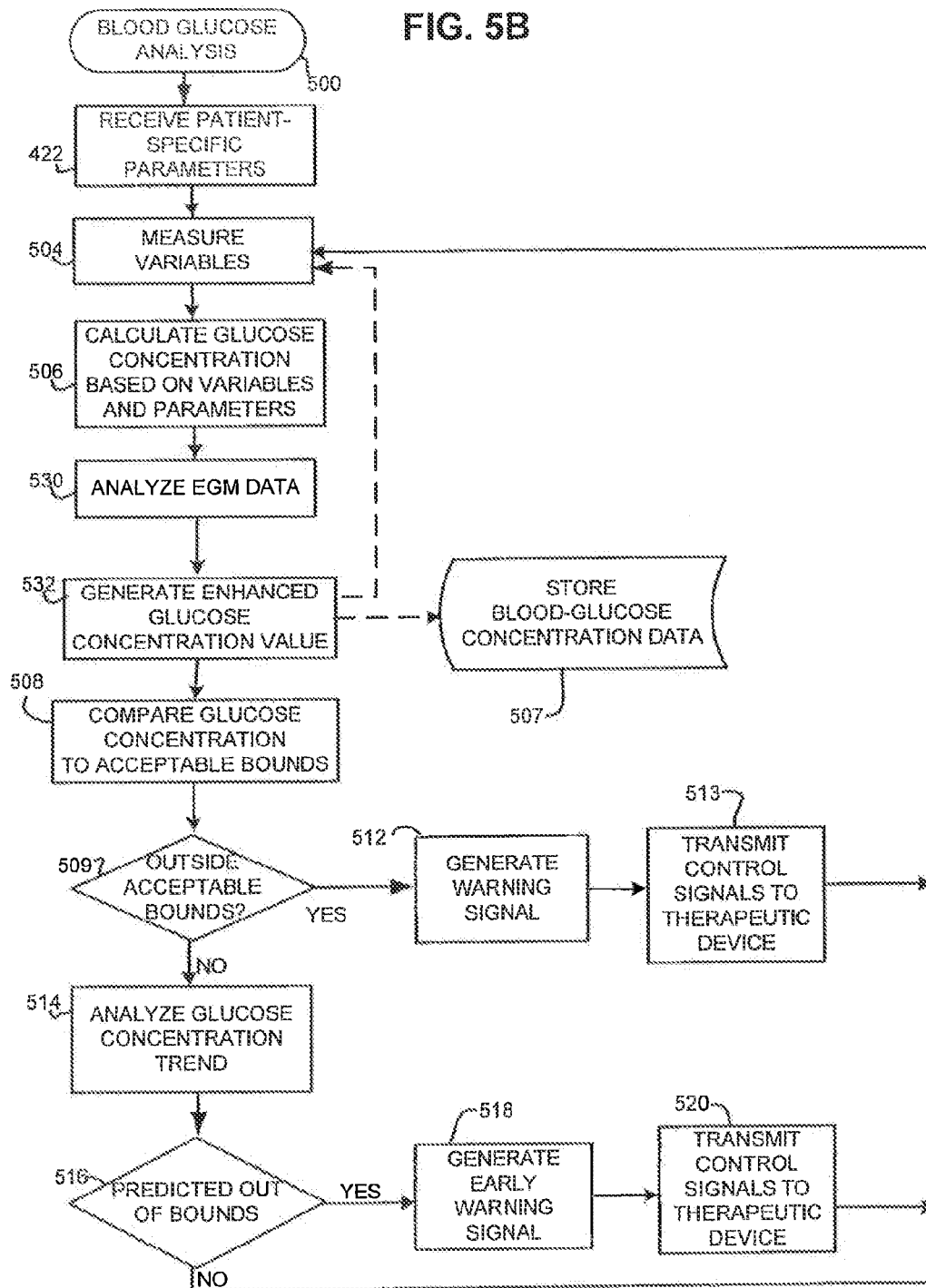


FIG. 5B



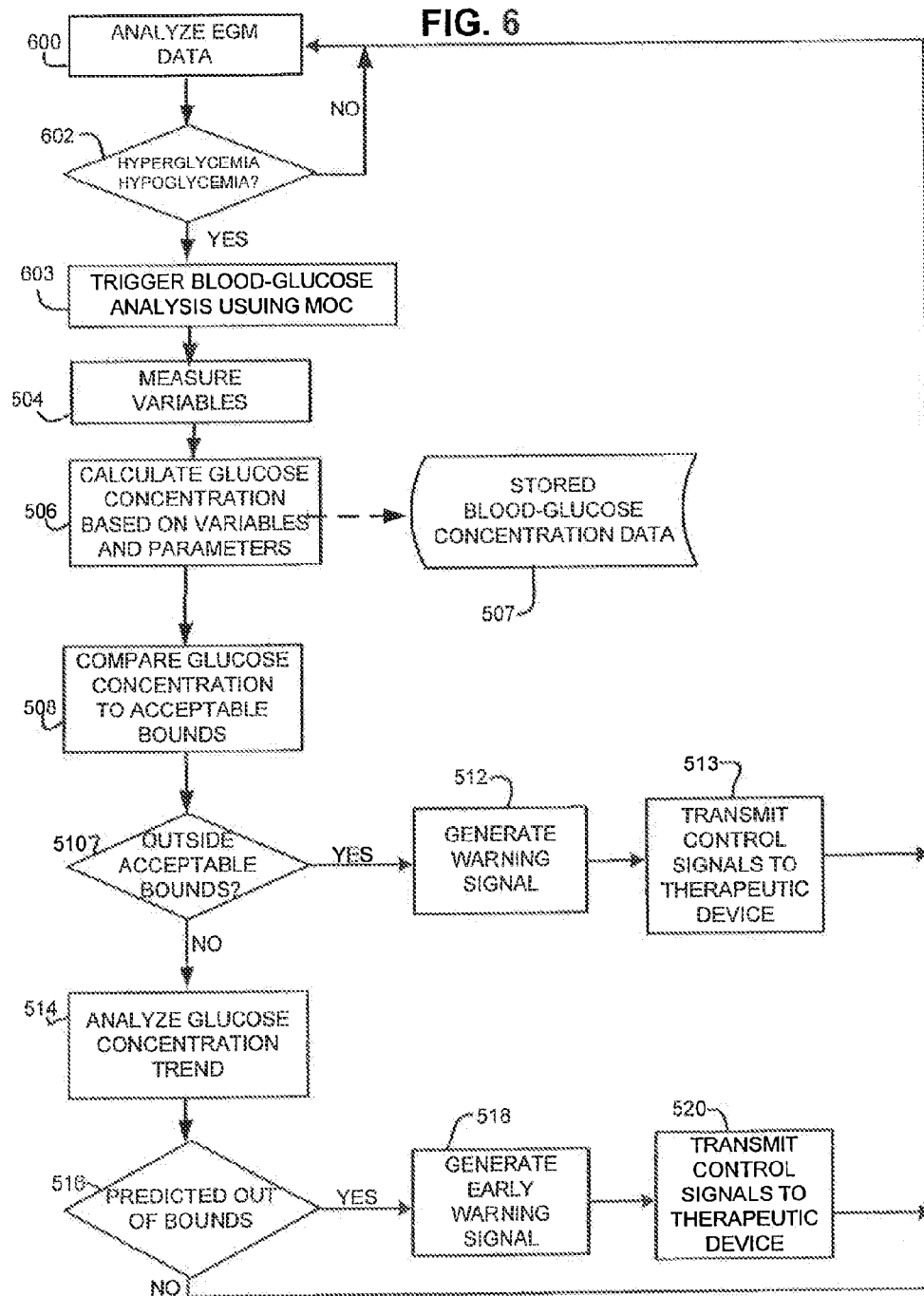


FIG. 7B

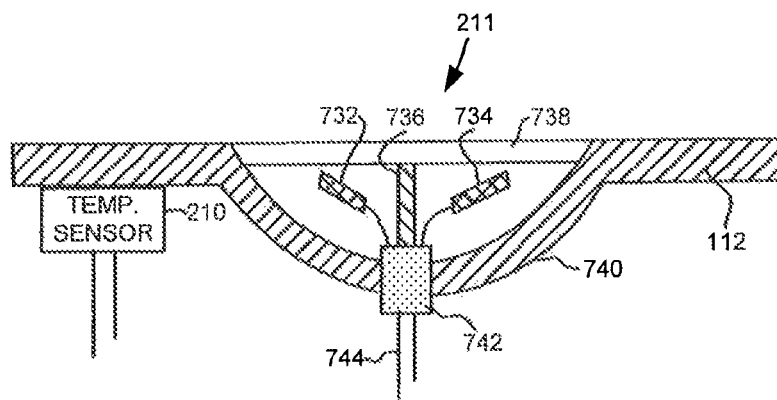
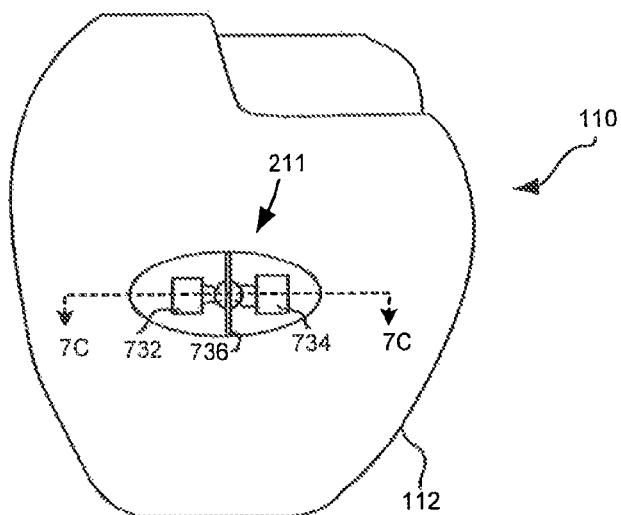


FIG. 7C

FIG. 8

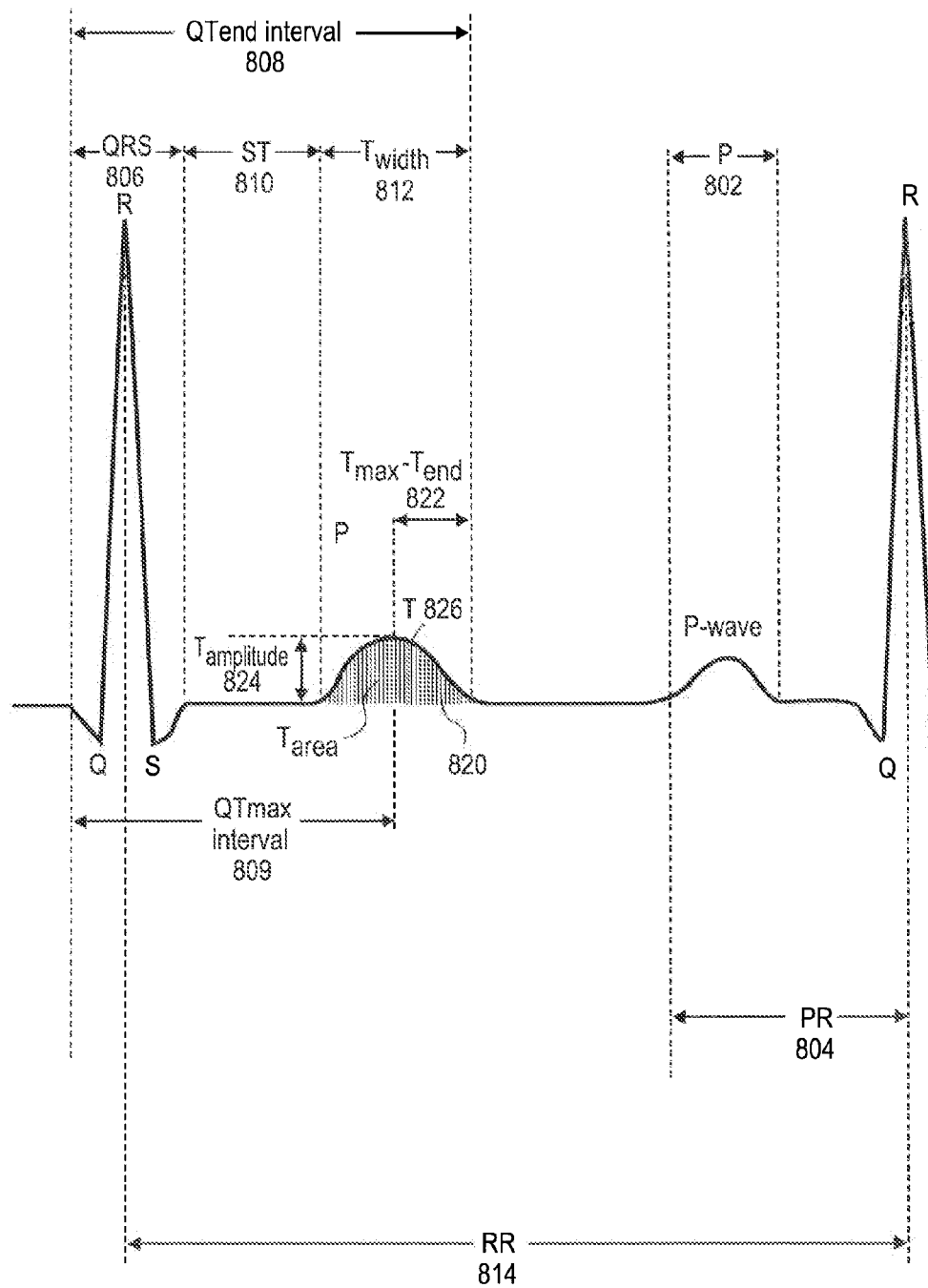


FIG. 9

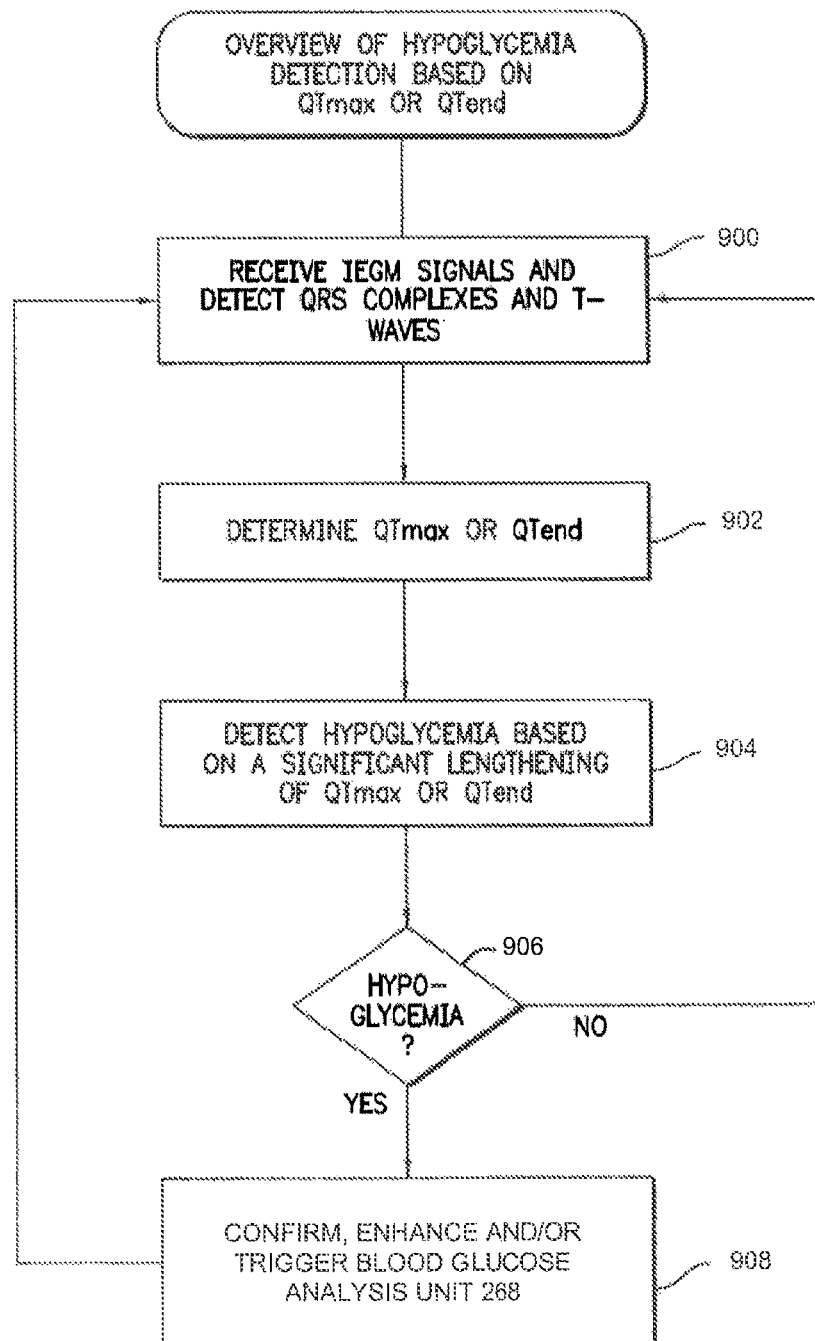


FIG. 10

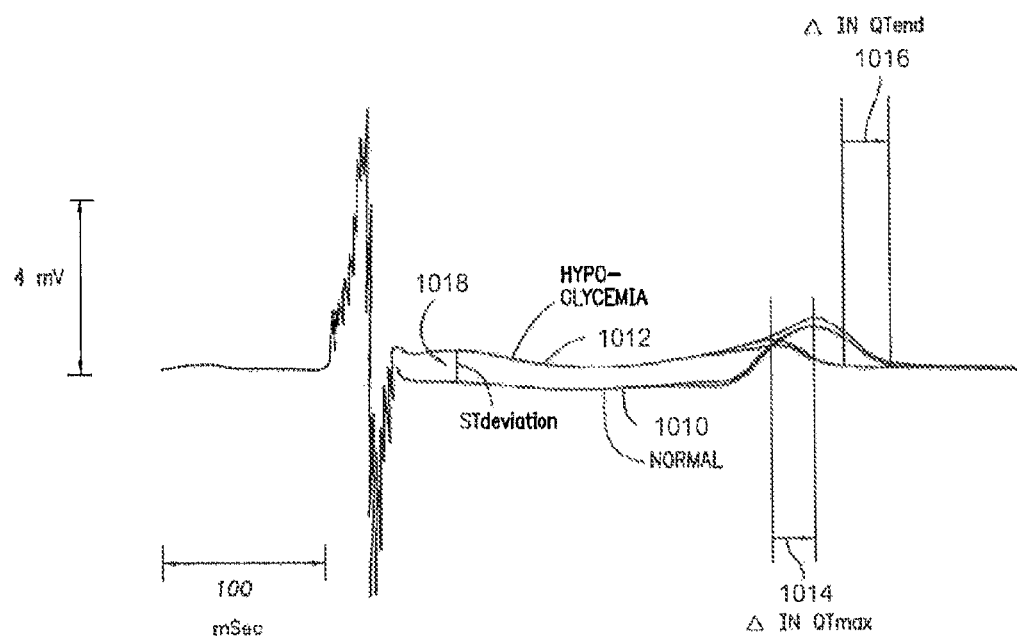


FIG. 11

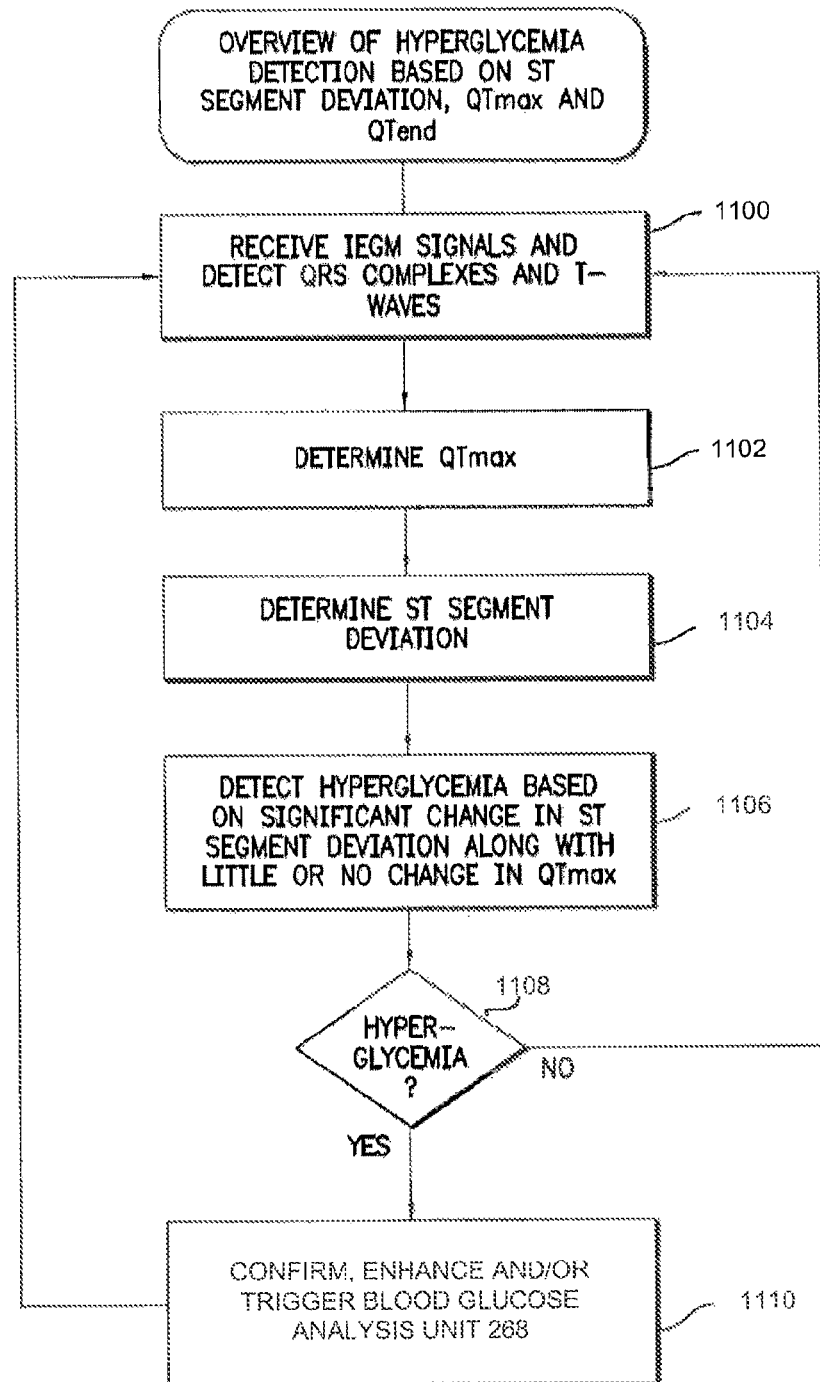


FIG. 12

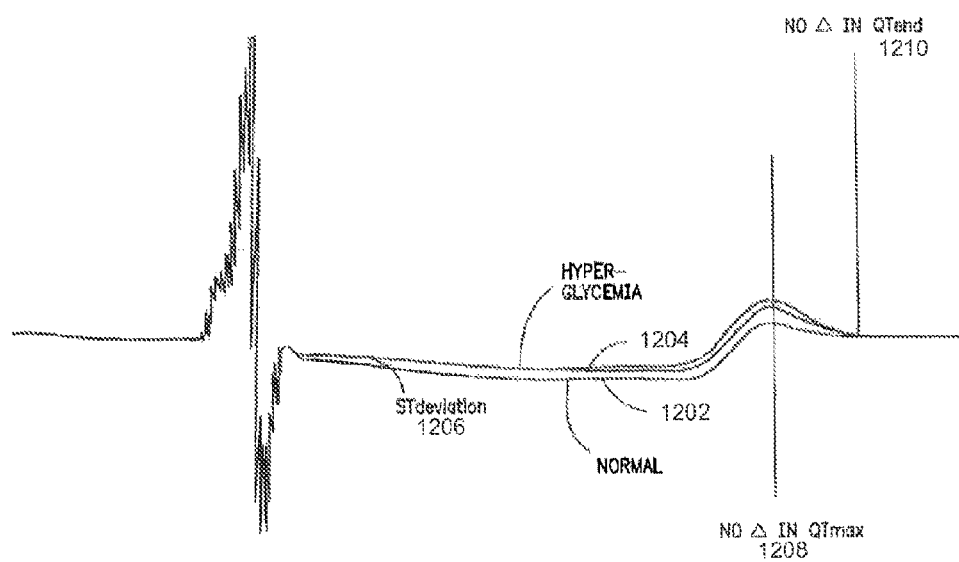


FIG. 13

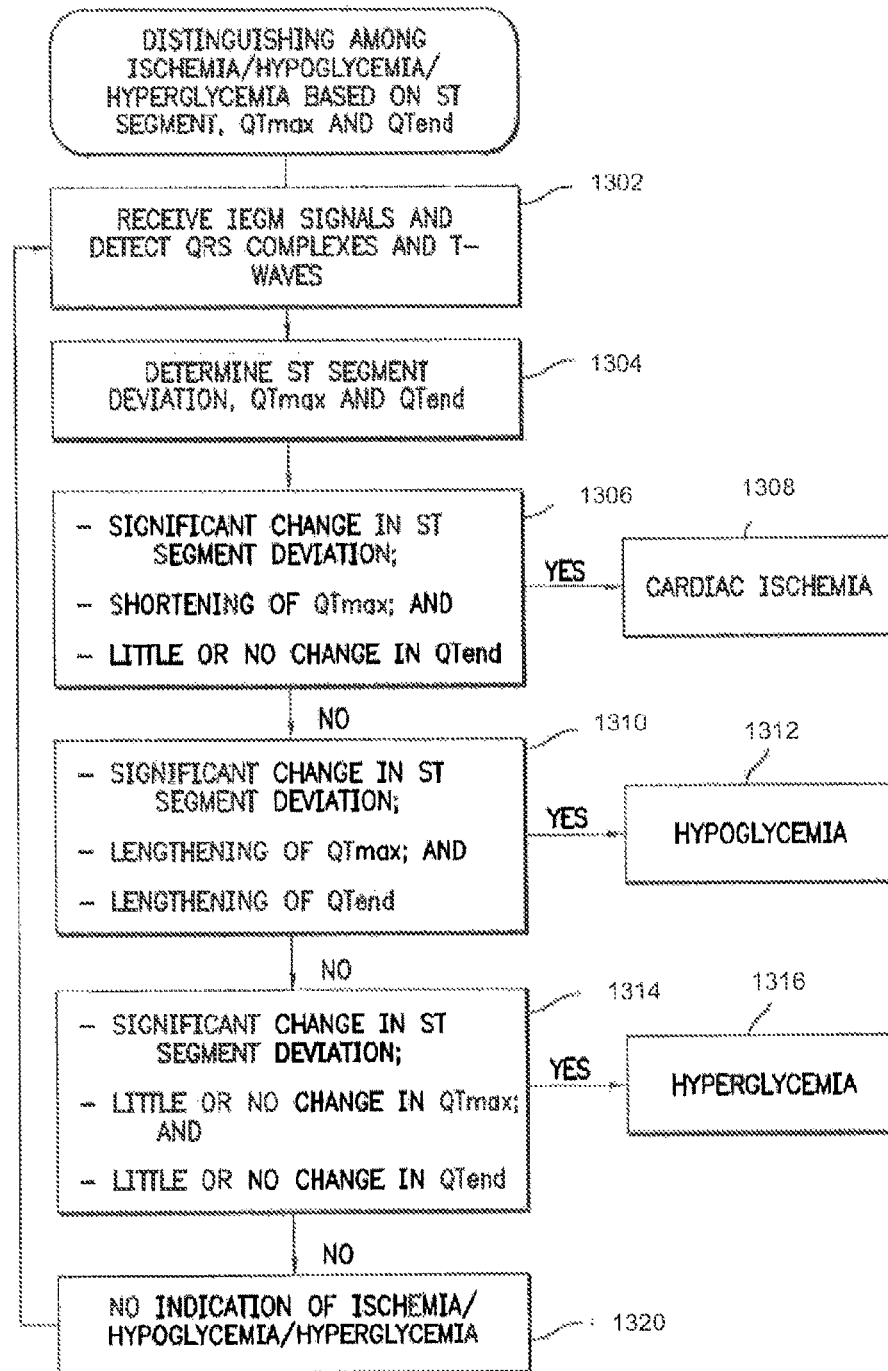


FIG. 14

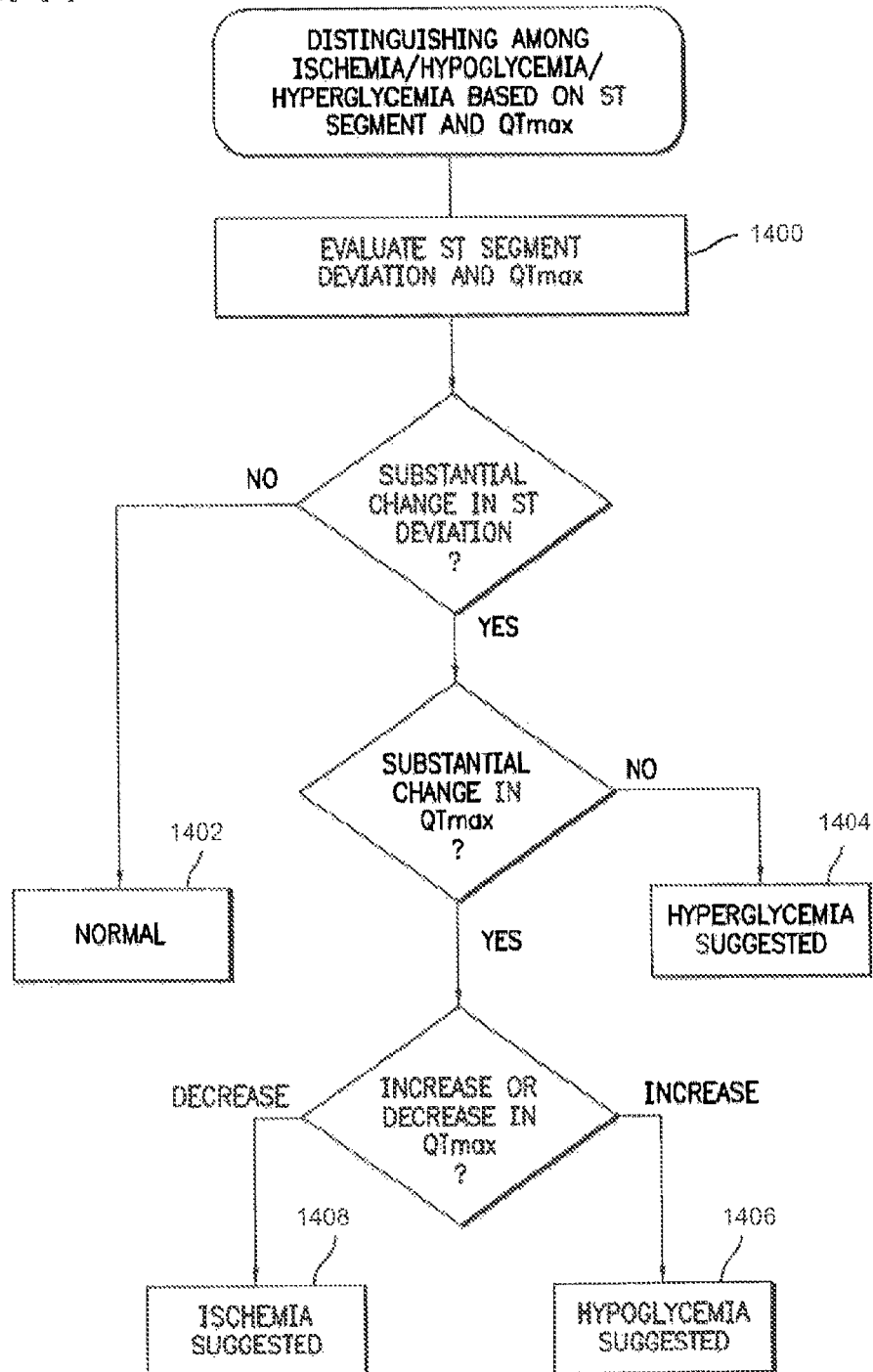
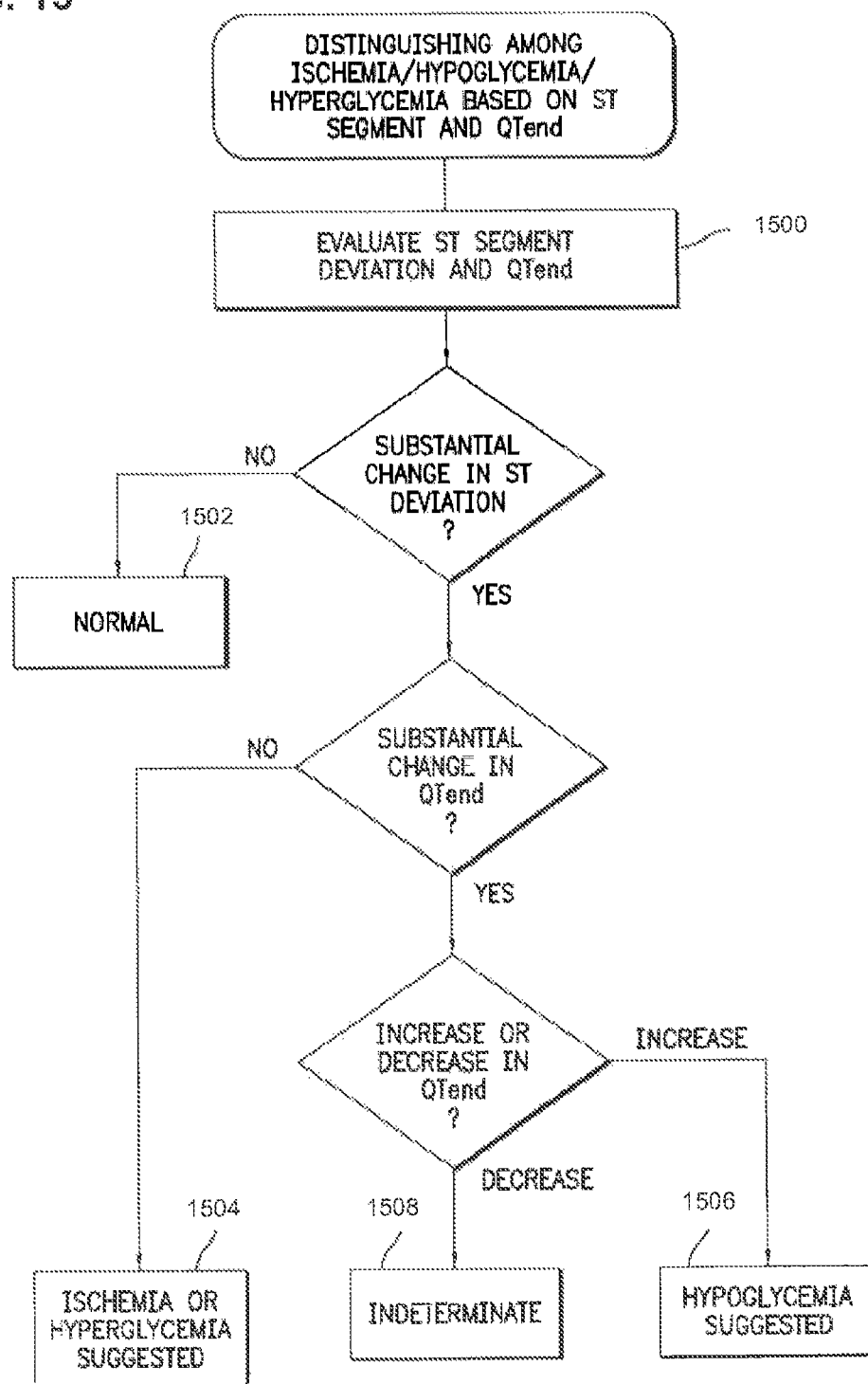


FIG. 15



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METHOD AND IMPLANTABLE SYSTEM FOR BLOOD-GLUCOSE CONCENTRATION MONITORING USING PARALLEL METHODOLOGIES

PRIORITY CLAIM

This application is a Continuation application of U.S. patent application Ser. No. 12/433,414, filed Apr. 30, 2009, entitled "METHOD AND IMPLANTABLE SYSTEM FOR BLOOD-GLUCOSE CONCENTRATION MONITORING USING PARALLEL METHODOLOGIES," now U.S. Pat. No. 8,630,692, which claims the benefit of U.S. Provisional Patent Application No. 61/164,798 entitled "METHOD AND IMPLANTABLE SYSTEM FOR BLOOD-GLUCOSE CONCENTRATION MONITORING USING PARALLEL METHODOLOGIES," filed Mar. 30, 2009. Each patent application identified above is incorporated herein by reference in its entirety to provide continuity of disclosure.

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is related to U.S. patent application Ser. No. 11/043,804 titled "System And Method For Distinguishing Among Cardiac Ischemia, Hypoglycemia And Hyperglycemia Using An Implantable Medical Device" to Gill et al., now U.S. Pat. No. 7,297,114, and U.S. patent application Ser. No. 11/615,591 titled "Method And Implantable System For Blood-Glucose Concentration Monitoring" to Wenzel et al., now U.S. Pat. No. 8,092,368, both of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Embodiments of the present invention relate to methods and implantable systems for using parallel methods to obtain measures of blood-glucose concentration.

BACKGROUND OF INVENTION

Cardiac disease has high comorbidity with diabetes. Up to 45% of individuals with bradycardia or tachycardia also suffer from diabetes. Diabetes is a life-long disease marked by high concentrations of glucose in the blood. The sugar called glucose enters the bloodstream when food is digested. Glucose is a source of fuel for the body. In response to the glucose in the bloodstream, an organ called the pancreas makes the hormone insulin. The role of insulin is to move glucose from the bloodstream into muscle, fat, and liver cells, where it can be used as fuel. Individuals with diabetes either do not produce insulin (Type I diabetes) or are resistant to insulin (Type II diabetes). Consequently, the concentration of glucose in the blood in a person with diabetes may vary by a large amount dependent upon what they have eaten and the person's metabolic requirements. Variation in blood-glucose concentration can cause adverse consequences for diabetics and individuals with cardiac disease.

Studies have suggested that hypoglycemia (abnormally low blood-glucose) may precipitate transient atrial fibrillation, arrhythmia and tachycardia. Collier et al., "Transient Atrial Fibrillation Precipitated By Hypoglycaemia: Two Case Reports," *Postgraduate Medical Journal* 63, 895-897 (1987); Shimada et al., "Arrhythmia During Insulin-Induced Hypoglycemia in a Diabetic Patient," *Arch. Intern. Med.* 144, 1068-9 (1984). It has been suggested that hypoglycemia-induced arrhythmia is a possible cause of sudden death during

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the sleep. Tattersall et al., "Unexplained Deaths of Type 1 Diabetic Patients," *Diabetic Med.* 8(1):49-58 (1991). Moreover some studies show that although implanted defibrillators can cause a significant reduction in mortality in high-risk cardiac disease patients they have less impact on the rate of sudden death in sleeping patients with cardiac disease—called "dead-in-bed" syndrome. It is suggested that such deaths are the result of untreated hypoglycemia and consequent arrhythmia. Moreover, when hypoglycemia is present, the resultant arrhythmia may be resistant to treatment by pacing. In one case study hypoglycemia triggered supraventricular tachycardia and an antitachycardia pacemaker was ineffective until the blood-glucose concentration was increased. Rokas et al., "Proarrhythmic Effects of Reactive Hypoglycemia," *Pace* 15, 373-376 (1992).

Blood-glucose concentration control is essential to the prevention of hypoglycemia and its adverse cardiac consequences. Blood-glucose concentration monitoring is the first step in blood-glucose concentration control. Typically, a sample of blood must be drawn and then the blood-glucose concentration assayed using color changing strips or an electrical device. To ensure proper dosage of insulin, individuals with diabetes use lancets to draw blood for conventional glucose measurements. A disadvantage of current blood-glucose concentration testing is that the painful process of drawing blood limits the number of times an individual is willing to take measurements. Even where external blood-glucose concentration monitoring does not require blood samples, it is still a disadvantage that the process requires active user intervention. Patients may forget to measure their blood-glucose concentration regularly and are not able to monitor their own blood-glucose concentration while sleeping.

A method for external monitoring of blood-glucose concentration without drawing blood is disclosed in a publication by Cho et al., entitled "Noninvasive Measurement of Glucose by Metabolic Heat Conformation Method," *Clinical Chemistry* 50:10 1894-1898 (2004), which is incorporated herein by reference. This publication utilizes a metabolic heat conformation method which depends upon measuring body surface temperature and conductive and radiative heat losses from the subject. These heat losses are tied through the circulatory system to glucose metabolism, which is the primary source of heat generation in the body. Using analysis of the surface temperature measurements and external peripheral measurements of blood flow, hematocrit and oxygen saturation, and standard blood-glucose concentration measurements, the authors developed relationships between the external measurements that predicted measured blood-glucose concentration. The MHC method utilizes precise measurements of external heat loss to estimate the rate of glucose metabolism and then correlates that to the blood-glucose concentration. However, while the method disclosed by Cho et al. has the advantage that it does not require blood to be drawn, it still requires active user intervention. See, also, U.S. Pat. No. 5,795,305 entitled "Process And Device For Non-Invasive Determination Of blood-glucose concentration In Parts Of The Human Body" to Cho et al.; and U.S. Pat. No. 5,924,996 titled "Process And Device For Detecting The Exchange Of Heat Between The Human Body And The Invented Device And Its Correlation To The blood-glucose concentration In Human Blood" to Cho et al., both of which are incorporated herein by reference. Moreover, the method disclosed by Cho, because it requires external measurements of the heat lost at the surface of the human body, cannot be utilized in an implantable device.

In view of the many disadvantages of conventional external blood-glucose concentration monitoring techniques,

implantable blood-glucose concentration monitors have been investigated. Such monitors typically require sensors for mounting directly within the blood stream. Most implantable glucose sensors that have been proposed are amperometric enzymatic biosensors which use immobilized glucose oxidase, an enzyme that catalyzes the oxidation of glucose to gluconic acid with the production of hydrogen peroxide. However, such amperometric enzymatic biosensors tend to clog very quickly. Thus, despite the demand for such a sensor, no implantable blood-glucose concentration sensor has yet achieved widespread use.

In view of the disadvantages of the state of the art with respect to glucose monitoring, it would be desirable to have an implantable system that could measure blood-glucose concentration reliably and accurately without the disadvantages of amperometric enzymatic biosensors.

SUMMARY OF INVENTION

In view of the background above and disadvantages of the state of the art, the present invention provides, in one embodiment, a method for calculating blood-glucose concentration using an implantable medical device implanted within a patient without the use of are amperometric enzymatic biosensor. The inventors have devised a metabolic oxygen conformation ("MOC") method which calculates blood-glucose concentration based upon its relationship to oxygen metabolism in the human body and is performed in parallel with other methods of determining blood-glucose concentration. The metabolic consumption of oxygen in the human body can be determined by measuring mixed venous oxygen concentration and cardiac output. Blood-glucose concentration is calculated based on the correlations between blood-glucose concentration and oxygen consumption along with other physiological variables such as heart-rate, blood flow, blood pressure and/or temperature. By using a combination of oxygen consumption and other variables, blood-glucose concentration can be reliably calculated throughout a wide range of concentrations. Blood-glucose concentration can also be monitored by analyzing EGM data. The results of both calculations are combined in a process for glucose monitoring thereby allowing self validation of blood-glucose analysis. Accordingly, the implantable system is capable of measuring blood-glucose concentration reliably and accurately without using amperometric enzymatic biosensors.

In a specific embodiment, the implantable medical device is a pacemaker or implantable stimulation device. Blood-glucose concentration monitoring is conveniently provided within patients already requiring a pacemaker or implantable stimulation device, without requiring implantation of additional devices. The combination of implantable stimulation device and implantable blood-glucose monitor is particularly useful because of the high comorbidity of diabetes and heart disease. Additionally, such implantable medical devices typically have the capability of sensing EGM data thus allowing for the blood-glucose concentration to be determined from the EGM data in parallel to other methods. Moreover, by using an implantable medical device to calculate blood-glucose concentration, no external monitoring device is required, no painful finger prick and no user intervention are needed. Hence, there is no risk the patient will fail to periodically measure blood-glucose concentration. Furthermore, blood-glucose concentration can be calculated as often as desired, for example, once every five minutes, allowing for more accurate control and also allowing for blood-glucose measurement when the patient is sleeping. Once the blood-glucose concentration has been calculated, the implantable

medical device compares the blood-glucose concentration against acceptable upper and lower bounds and generates appropriate warning signals if the concentration is outside the acceptable bounds. If an implantable insulin pump or other therapeutic device is provided, the insulin pump or other therapeutic device may be automatically controlled in response to the calculated blood-glucose concentration to maintain normoglycemia (the presence of a normal blood-glucose concentration).

In a specific embodiment, or implantable cardiac stimulation device such as a pacemaker, implantable defibrillator or other cardiac rhythm management device is provided with sensors to monitor properties of oxygen metabolism such as cardiac output, core and peripheral temperature, mixed venous oxygen concentration and arterial oxygen concentration. Cardiac output can be determined using the pacemaker electrodes. Stroke volume can be calculated e.g. from the time variation of the bioimpedance between the tip of an intracardial electrode and the metallic housing of a pacemaker. The heart-rate is also monitored by the pacemaker. Cardiac output can then be calculated based on heart-rate and stroke volume. One or more implantable oxymeters are used to measure the oxygen concentration of mixed venous blood and the oxygen concentration in arterial blood. Using the cardiac output and the difference between the arterial and venous oxygen concentration, the metabolic oxygen consumption can be calculated by performing a Fick calculation: $\text{oxygen consumption} = \text{cardiac output} \times (\text{arterial oxygen concentration} - \text{venous oxygen concentration})$. In the exemplary embodiment, the pacemaker or implantable stimulation device is provided with a control unit which utilizes the cardiac output, temperature, and blood-oxygen data in combination with stored information regarding the relationship of the cardiac output, temperature, and blood-oxygen data to blood-glucose concentration in accordance with the metabolic oxygen conformation method. By using a combination of oxymetric, temperature, and electrocardiographic data, a metric of blood-glucose concentration can be reliably calculated throughout a wide range of concentrations. Analysis of EGM data from the pacemaker electrodes is used in a parallel method to calculate another metric of blood-glucose concentration. The blood-glucose concentration metric calculated from EGM data is used to validate or confirm the results of the other blood-glucose concentration analysis.

In accordance with specific embodiments of the invention, techniques are provided for use with an implantable medical device for monitoring blood-glucose concentration and detecting or confirming hyperglycemia, normoglycemia and/or hypoglycemia using analysis of EGM data. In an exemplary embodiment, the device tracks changes over time in deviations in the ST segment, QTmax and/or QTend. The device detects the onset of a hypoglycemia based on any significant lengthening of QTmax and/or QTend. Preferably, the device also uses deviations in the ST segment to improve detection specificity. As noted, hypoglycemia typically causes a significant ST deviation. Hence, if a significant ST deviation is detected along with a lengthening of QTmax or QTend, the detection of hypoglycemia is confirmed. The device detects the onset of a hyperglycemia based on any significant ST deviation combined with little or no change in QTmax. To provide increased specificity, ST deviation, QTmax and QTend are preferably all used. The following table summarizes changes in the ST segment, QTmax and QTend in response to hypoglycemia, and hyperglycemia that are exploited by embodiments of the invention.

TABLE I

	ST Segment	QTmax	QTend
Hypoglycemia	Significant deviation	Lengthens	Lengthens
Hyperglycemia	Significant deviation	Little or no change	Little or no change
Normoglycemia	No significant deviation	Little or no change	Little or no change

In specific embodiments, after the blood-glucose concentration has been calculated, an implantable medical device compares the blood-glucose concentration against upper and lower acceptable bounds and appropriate warning signals are generated if the concentration falls outside the acceptable bounds. In one example, wherein an implantable insulin pump is additionally provided, the delivery of insulin is regulated in response to the calculated blood-glucose concentration to maintain blood-glucose concentration within an acceptable range.

Thus, various techniques are provided for monitoring blood-glucose concentration based on the metabolic oxygen conformation method in combination with analysis of the EGM. The monitoring and control of glucose concentrations facilitated by the invention is beneficial to diabetics as well as subjects who have not been diagnosed as diabetic. Other objects, features and advantages of the invention will be apparent from the detailed description to follow.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and further features, advantages and benefits of the present invention will be apparent upon consideration of the present description taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a simplified, partly cutaway view illustrating an implantable stimulation device in electrical communication with at least three leads implanted into a patient's heart for delivering multi-chamber stimulation and shock therapy;

FIG. 2 is a functional block diagram of the multi-chamber implantable stimulation device of FIG. 1, illustrating the basic elements that provide cardioversion, defibrillation and/or pacing stimulation in four chambers of the heart and illustrating a blood-glucose concentration monitoring unit for automatically calculating blood-glucose concentration from oxymetric, temperature, and electrocardiographic measurements in accordance with specific embodiments of the present invention;

FIG. 3 is a functional block diagram illustrating components of a programmer for use in programming the implantable device of FIGS. 1 and 2, and in particular illustrating a calibration system for use in calibrating the blood-glucose concentration monitoring unit of the implantable device in accordance with specific embodiments of the present invention;

FIG. 4 is a flowchart illustrating a calibration technique performed by both the implantable stimulation device of FIG. 2 and the external programmer of FIG. 3 following implantation of the device for determining patient-specific parameters exploited by the technique of FIG. 5 in accordance with specific embodiments of the present invention;

FIG. 5A is a flow diagram illustrating a method performed by the blood-glucose analysis unit of FIG. 2 to calculate blood-glucose concentration in accordance with a specific embodiment of the present invention;

FIG. 5B is a flow diagram illustrating a method performed by the blood-glucose analysis unit of FIG. 2 to calculate

blood-glucose concentration in accordance with another specific embodiment of the present invention;

FIG. 6 is a flow diagram illustrating a method performed by the blood-glucose analysis unit of FIG. 2 to calculate blood-glucose concentration in accordance with another specific embodiment of the present invention;

FIG. 7A shows an exemplary oxymeter suitable for use in the implantable stimulation device of FIGS. 1 and 2;

FIG. 7B shows an exemplary photoplethysmography sensor for use in the implantable stimulation device of FIGS. 1 and 2;

FIG. 7C shows a sectional view of the photoplethysmography sensor of FIG. 7B;

FIG. 8 is a graph providing a stylized representation of the EGM of a single heartbeat, particularly illustrating the QTmax interval;

FIG. 9 is a flow chart providing an overview of an exemplary method performed by a hypoglycemia detection/confirmation system of FIG. 2 for detecting/confirming hypoglycemia based primarily on a significant lengthening of either QTmax or QTend;

FIG. 10 is a graph providing exemplary representations of the EGM of a single heartbeat, particularly illustrating a significant lengthening of both QTmax and QTend;

FIG. 11 is a flow chart providing an overview of an exemplary method performed by a hyperglycemia detection/confirmation system of FIG. 2 for detecting/confirming hyperglycemia based primarily on a significant deviation in the ST segment along with little or no change in QTmax;

FIG. 12 is a graph providing exemplary representations of the EGM of a single heart beat, particularly illustrating a significant deviation in ST segment caused by hyperglycemia, along with little or no change in QTmax;

FIG. 13 is a flow chart providing an overview of an exemplary method performed by the implantable device of FIG. 2 for distinguishing and confirming hypoglycemia and hyperglycemia based on ST segment, QTmax, and QTend;

FIG. 14 is a flow chart providing an overview of an exemplary method performed by the implantable device of FIG. 2 for distinguishing and confirming hypoglycemia and hyperglycemia based on ST segment deviation and QTmax; and

FIG. 15 is a flow chart providing an overview of an exemplary method performed by the implantable device of FIG. 2 for distinguishing and confirming hypoglycemia and hyperglycemia based on ST segment deviation and QTend.

DETAILED DESCRIPTION

The following description is of the best modes presently contemplated for practicing various embodiments of the present invention. The description is not to be taken in a limiting sense but is made merely for the purpose of describing the general principles of the invention. The scope of the invention should be ascertained with reference to the claims. In the description of the invention that follows, like numerals or reference designators will be used to refer to like parts or elements throughout. In addition, the left-most digit of a reference number identifies the drawing in which the reference number first appears.

This detailed description is organized in sections as follows:

1. Implantable Stimulation Device;
2. Programmer;
3. Metabolic Oxygen Conformation Method For Blood-Glucose Analysis;
4. Method For Enhanced Blood-Glucose Analysis Using Metabolic Oxygen Conformation and EGM;

5. Oxymetry and PPG Sensors;
6. Detection/Confirmation of Hypoglycemia and Hyperglycemia Based on EGM;
- 6(a) Detection/Confirmation of Hypoglycemia Based on QTmax and/or QTend;
- 6(b) Detection/Confirmation of Hyperglycemia Based on STdeviation, QTmax and/or QTend; and
- 6(c) Detection/Confirmation of Hypoglycemia and Hyperglycemia Based on ST deviation QTmax and QTend.

Section 1 describes an exemplary implantable stimulation device that is capable of performing blood-glucose analysis in accordance with specific embodiments of the present invention. Section 2 describes a programmer which can be used in conjunction with the implantable stimulation device. Section 3 describes methods for analyzing blood-glucose concentration using the metabolic oxygen conformation method to generate a first metric of blood-glucose concentration. Section 4 describes a method for generating an enhanced metric of blood-glucose concentration by using the first metric of blood-glucose concentration in conjunction with a second metric of blood-glucose concentration derived from analysis of the EGM in accordance with specific embodiments of the present invention. Section 5 describes exemplary oxymetry and PPG sensors which may be used in connection with the metabolic oxygen conformation method. Section 6 and sub-sections 6(a), 6(b) and 6(c) describe exemplary methods of analyzing the EGM to provide the second metric of blood-glucose concentration.

1. Implantable Stimulation Device

FIG. 1 illustrates an exemplary implantable stimulation device **110** capable of determining blood-glucose concentration utilizing the metabolic oxygen concentration method and EGM analysis in accordance with specific embodiments of the present invention. Implantable stimulation device **110** is in electrical communication with a patient's heart **100** by way of four leads **120**, **130**, **140** and **150** suitable for multi-chamber sensing, stimulation and shock therapy. This system allows for sensing and/or stimulation in all four chambers of the heart including: right atrium **102**, right ventricle **104**, left atrium **106** and left ventricle **108**.

To sense atrial cardiac signals and to provide right atrial chamber stimulation therapy, implantable stimulation device **110** is coupled to an implantable right atrial lead **120** having at least an atrial tip electrode **122**, which typically is implanted in the patient's right atrial appendage. In accordance with one embodiment of the present invention, right atrial lead **120** also comprises an oxymeter **124** for measuring mixed-venous oxygen saturation.

To sense left atrial and ventricular cardiac signals and to provide left-chamber stimulation therapy, implantable stimulation device **110** is coupled to a "coronary sinus" lead **140** designed for placement in the "coronary sinus region" **105** via the coronary sinus so as to place a distal electrode adjacent to the left ventricle **108** and additional electrode(s) adjacent to the left atrium **106**. As used herein, the phrase "coronary sinus region" **105** refers to the vasculature of the left ventricle, including any portion of the coronary sinus, great cardiac vein, left marginal vein, left posterior ventricular vein, middle cardiac vein, and/or small cardiac vein or any other cardiac vein accessible by the coronary sinus. Accordingly, the coronary sinus lead **140** is designed to receive atrial and ventricular cardiac signals and to deliver left ventricular pacing therapy using at least a left ventricular tip electrode **142**, left atrial pacing therapy using at least a left atrial ring electrode **144**, and shocking therapy using at least a left atrial coil electrode **146**.

Implantable stimulation device **110** is also shown in communication with the patient's heart **100** by way of an implantable left atrial lead **150** having in this embodiment, a left atrial sensor **152** implanted in the septum **103** between the right atrium **102** and left atrium **106**. Left atrial sensor **152** is in one embodiment comprises a hermetically-sealed pressure transducer module. In one embodiment, the implantable module comprises a proximal anchor and a distal anchor which are configured to sandwich an atrial septum wall **103** (or the left atrial free wall, the pulmonary vein wall, or any other suitable wall of a heart or a blood vessel) between the proximal anchor leg and the distal anchor leg and to support the module in the septum wall **103**. In one embodiment, the sensor module comprises one or more sensors in addition to a pressure transducer at its distal end. These sensors may include a plurality of pressure transducers to measure pressures in the transmural space or locations proximal to the transmural space, or to measure differential pressure between the distal diaphragm and another location. Other types of sensors include, but are not limited to, temperature sensors, electrodes for measuring electrical activity, and oxymeters. In one embodiment, the sensor module contains at least one electrode for stimulating the organ in which it is placed. For example, such an electrode or electrodes may be used for electrical pacing the left atrium. A suitable embodiment of a lead-mounted left atrial sensor is the Savacor HEARTPOD™ which in the present application is connected via lead **150** to implantable stimulation device **110**. Details of such left atrial sensor modules may be found in U.S. patent application Ser. No. 11/115,991 entitled, "Implantable Pressure Transducer System Optimized For Anchoring And Positioning" filed Apr. 27, 2005 to Eigler et al.; Ser. No. 10/270,784 entitled "Permanently Implantable System And Method For Detecting, Diagnosing And Treating Congestive Heart Failure" filed: Oct. 11, 2002 to Eigler et al.; and Ser. No. 11/027,598 entitled "Flexible Lead For Digital Cardiac Rhythm Management" filed: Dec. 30, 2004 to Mann et al. all of which are incorporated herein by reference.

Implantable stimulation device **110** is also shown in electrical communication with the patient's heart **100** by way of an implantable right ventricular lead **130** having, in this embodiment, a right ventricular tip electrode **132**, a right ventricular ring electrode **134**, a right ventricular (RV) coil electrode **136**, and an SVC coil electrode **138**. Typically, the right ventricular lead **130** is transvenously inserted into the heart **100** so as to place the right ventricular tip electrode **132** in the right ventricular apex so that the RV coil electrode **136** will be positioned in the right ventricle and the SVC coil electrode **138** will be positioned in the superior vena cava. Accordingly, the right ventricular lead **130** is capable of receiving cardiac signals, and delivering stimulation in the form of pacing and shock therapy to the right ventricle. In accordance with one embodiment of the present invention, the time-varying impedance between an electrode in the right ventricle and the body of implantable stimulation device **110** is used to calculate cardiac stroke volume.

FIG. 2 illustrates a simplified block diagram of the multi-chamber implantable stimulation device **110** which is capable of measuring blood-glucose concentration and treating both fast and slow arrhythmias with stimulation therapy, including cardioversion, defibrillation, and pacing stimulation. While a particular multi-chamber device is shown, this is for illustration purposes only and one of skill in the art could readily duplicate, eliminate or disable the appropriate circuitry in any desired combination to provide a device capable of measuring blood-glucose concentration with or without treating the heart with cardioversion, defibrillation and/or pacing stimulation.

Referring again to FIG. 2, implantable stimulation device 110 includes a housing 112 which is often referred to as a “can”, “case” or “case electrode”, and which may be programmably selected to act as the return electrode for all “unipolar” modes. Housing 112 may further be used as a return electrode alone or in combination with one or more of the coil electrodes 146, 136, or 138, for shocking purposes. Housing 112 further includes a connector (not shown) having a plurality of terminals, 242, 243, 244, 245, 246, 247, 248, 249, 252, 254, 256, and 258 (shown schematically and, for convenience, the names of the electrodes to which they are connected are shown next to the terminals). To achieve right atrial sensing and pacing, the connector includes at least a right atrial tip terminal 242 adapted for connection to the right atrial (AR) tip electrode 122, a right atrial oxymeter terminal 243 adapted for connection to the oxymeter 124. To achieve left chamber sensing, pacing and/or shocking, the connector includes at least a left ventricular (VL) tip terminal 244, a left atrial sensor terminal, 245, a left atrial (AL) ring terminal 246, and a left atrial (AL) shocking terminal (coil) 248, which are adapted for connection to the left ventricular tip electrode 142, the left atrial sensor 152, the left atrial ring electrode 144, and the left atrial coil electrode 146, respectively. To support right chamber sensing, pacing and/or shocking, the connector further includes a right ventricular (VR) tip terminal 252, a right ventricular (VR) ring terminal 254, a right ventricular (RV) shocking terminal (coil) 256, and an SVC shocking terminal (coil) 258, which are adapted for connection to the right ventricular tip electrode 132, right ventricular ring electrode 134, the RV coil electrode 136, and the SVC coil electrode 138, respectively. The connector may also include one or more I/O terminals 247, 249 for communicating with optional implantable devices external to housing 112.

At the core of implantable stimulation device 110 is a programmable host controller 260 which controls the various modes of stimulation therapy and performs calculations of blood-glucose concentration. As is well known in the art, host controller 260 may be a microcontroller and typically includes a microprocessor or equivalent control circuitry or processor, designed specifically for controlling the delivery of stimulation therapy, and may further include RAM or ROM memory, logic and timing circuitry, state machine circuitry, and I/O circuitry. Typically, host controller 260 includes the ability to process or monitor input signals (data) as controlled by program code stored in a designated block of memory. Host controller 260 includes the ability to calculate blood-glucose concentration from measured oxymetric, temperature, and electrocardiographic variables and stored parameters. The details of the design and operation of host controller 260 are not critical to embodiments of the present invention. Rather, any suitable host controller 260 may be used that carries out the functions described herein. The use of microprocessor-based control circuits for performing timing and data analysis functions is well known in the art.

As shown in FIG. 2, an atrial pulse generator 270 and a ventricular pulse generator 272 generate pacing stimulation pulses for delivery by right atrial lead 120, right ventricular lead 130, and/or coronary sinus lead 140 via a switch bank 274. It is understood that in order to provide stimulation therapy in each of the four chambers of the heart, atrial pulse generator 270 and ventricular pulse generator 272 may include dedicated, independent pulse generators, multiplexed pulse generators, or shared pulse generators. Atrial pulse generator 270 and ventricular pulse generator 272 are controlled by host controller 260 via appropriate control signals 276 and 278, respectively, to trigger or inhibit the stimulation pulses.

Host controller 260 further includes pacing control circuitry 262 which is used to control the timing of such stimulation pulses (e.g., pacing rate, atrio-ventricular (A-V) delay, atrial interconduction (A-A) delay, ventricular interconduction (V-V) delay, pacing mode, etc.), as well as to keep track of the timing of refractory periods, PVARP intervals, noise detection windows, evoked response windows, alert intervals, marker channel timing, etc.

Implantable stimulation device 110 may operate as an implantable cardioverter/defibrillator (ICD) device. That is, it may detect the occurrence of an arrhythmia, and automatically apply an appropriate electrical shock therapy to the heart aimed at terminating the detected arrhythmia. To this end, host controller 260 further controls a shocking circuit 216 by way of a control signal 218. The shocking circuit 216 generates shocking pulses of low (up to 0.5 joules), moderate (0.5-10 joules), or high (11-40 joules) energy, as controlled by the host controller 260. Such shocking pulses are applied to the patient's heart through at least two shocking electrodes, as shown in this embodiment, selected from left atrial coil electrode 146, RV coil electrode 136, and/or SVC coil electrode 138 (FIG. 1). As noted above, housing 112 may act as an active electrode in combination with the RV electrode 136, or as part of a split electrical vector using SVC coil electrode 138 or left atrial coil electrode 146 (e.g., using the RV electrode as a common electrode).

Switch bank 274 includes a plurality of electrically-configurable switches for connecting the desired electrodes to the appropriate I/O circuits, thereby providing complete electrode programmability. Accordingly, switch bank 274, in response to a control signal 280 from host controller 260, determines the polarity of the stimulation pulses (e.g., unipolar, bipolar, combipolar, etc.) by selectively closing the appropriate combination of switches (not shown) as is known in the art. If multiple RV electrodes are employed to generate a single averaged ventricular signal, then switch bank 274 is configured to allow the paralleling (or averaging) of the multiple RV electrodes to simulate a large electrode for accurate sensing of the T-wave.

Atrial sensing circuits 282 and ventricular sensing circuits 284 may also be selectively coupled to right atrial lead 120, coronary sinus lead 140, and right ventricular lead 130, through the switch bank 274, for detecting the presence of cardiac activity in each of the four chambers of the heart. Accordingly, the atrial and ventricular sensing circuits 282 and 284 may include dedicated sense amplifiers, multiplexed amplifiers, or shared amplifiers. Switch bank 274 determines the “sensing polarity” of the cardiac signal by selectively closing the appropriate switches. In this way, the clinician may program the sensing polarity independent of the stimulation polarity.

Each of the sensing circuits, 282 and 284, preferably employ one or more low power, precision amplifiers with programmable gain and/or automatic gain control, bandpass filtering, and a threshold detection circuit, to selectively sense the cardiac signal of interest. The automatic gain control enables implantable stimulation device 110 to deal effectively with the difficult problem of sensing the low amplitude signal characteristics of atrial or ventricular fibrillation.

The outputs of the atrial and ventricular sensing circuits 282 and 284 are connected to host controller 260 for triggering or inhibiting the atrial and ventricular pulse generators 270 and 272, respectively, in a demand fashion, in response to the absence or presence of cardiac activity, respectively, in the appropriate chambers of the heart. The atrial and ventricular sensing circuits 282 and 284, in turn, receive control signals over signal lines 286 and 288 from host controller 260, for

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controlling the gain, threshold, polarization charge removal circuitry (not shown), and the timing of any blocking circuitry (not shown) coupled to the inputs of the atrial and ventricular sensing circuits **282** and **284**.

For arrhythmia detection, implantable stimulation device **110** utilizes the atrial and ventricular sensing circuits **282** and **284** to sense cardiac signals, for determining whether a rhythm is physiologic or pathologic. As used herein “sensing” is reserved for the noting of an electrical signal, and “detection” is the processing of these sensed signals and noting the presence of an arrhythmia. The timing intervals between sensed events (e.g., P-waves, R-waves, and depolarization signals associated with fibrillation which are sometimes referred to as “F-waves” or “Fib-waves”) are then classified by the host controller **260** by comparing them to a predefined rate zone limit (e.g., bradycardia, normal, low rate VT, high rate VT, and fibrillation rate zones) and various other characteristics (e.g., sudden onset, stability, physiologic sensors, and morphology, etc.) in order to determine the type of remedial therapy that is needed (e.g., bradycardia pacing, anti-tachycardia pacing, cardioversion shocks or defibrillation shocks, collectively referred to as “tiered therapy”).

Cardiac signals are also applied to the inputs of an analog-to-digital (A/D) data acquisition unit **290**. Data acquisition unit **290** is configured to acquire intracardiac electrogram signals, convert the raw analog data into digital signals, and store the digital signals for later processing and/or telemetric transmission to an external device **202**. Data acquisition unit **290** is coupled to right atrial lead **120**, the coronary sinus lead **140**, the right ventricular lead **130**, and the left atrial lead **150** through the switch bank **274** to sample cardiac signals across any pair of desired electrodes.

Advantageously, data acquisition unit **290** may be coupled to host controller **260** or other detection circuitry, for detecting an evoked response from the heart **100** in response to an applied stimulus, thereby aiding in the detection of “capture”. Capture occurs when an electrical stimulus applied to the heart is of sufficient energy to depolarize the cardiac tissue, thereby causing the heart muscle to contract. Host controller **260** detects a depolarization signal during a window following a stimulation pulse, the presence of which indicates that capture has occurred. Host controller **260** enables capture detection by triggering the ventricular pulse generator **272** to generate a stimulation pulse, starting a capture detection window using the timing circuitry within host controller **260**, and enabling data acquisition unit **290** via control signal **292** to sample the cardiac signal that falls in the capture detection window and, based on the amplitude of the sampled cardiac signal, determines if capture has occurred. The implementation of capture detection circuitry and algorithms are well known. See for example, U.S. Pat. No. 4,729,376 (Decote, Jr.); U.S. Pat. No. 4,708,142 (Decote, Jr.); U.S. Pat. No. 4,686,988 (Sholder); U.S. Pat. No. 4,969,467 (Callaghan et. al.); and U.S. Pat. No. 5,350,410 (Mann et. al.), which patents are hereby incorporated herein by reference. The type of capture detection unit used is not critical to the present invention.

Implantable stimulation device **110** may also include one or more host sensors **208**, which can be located within the housing **112** of implantable stimulation device **110** as shown, or can be located external to the housing. These sensors can include, by way of example, blood flow sensors, temperature sensors, and blood pressure sensors. Host sensors **208** may include a physiologic sensor **209**, a temperature sensor **210** and a PPG sensor **211**. As shown in FIG. 2, host sensors **208** may be connected to via switch bank **274** to host controller **260** directly or through data acquisition unit **290** such that

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host controller **260** can receive measurements of the physiological variables from the host sensors **208**.

Physiologic sensor **209** is commonly referred to as a “rate-responsive” sensor because it is typically used to adjust pacing stimulation rate according to the exercise state of the patient. However, the rate-responsive sensor may also be used to detect changes in cardiac output, changes in the physiological condition of the heart, or diurnal changes in activity (e.g., detecting sleep and wake states). Accordingly, host controller **260** responds to the rate-responsive sensor by adjusting the various pacing parameters (such as rate, AV Delay, V-V Delay, etc.) at which the atrial and ventricular pulse generators, **270** and **272**, generate stimulation pulses.

Temperature sensor **210** may comprise any electronic device for measuring temperature. Suitable devices include, but are not limited to, thermopiles, thermistors, thermocouples. Thermopiles measure temperature by measuring IR radiation incident of the detector surface. Thus, if a thermopile is used as temperature sensor **210**, a window transparent to IR (not shown) should be provided to allow heat/IR radiation from the blood to fall on the surface of the detector. Thermistors and thermocouples may measure temperature by conduction. Such temperature measuring devices should therefore be placed in good thermal contact with the blood. As shown in FIG. 2, temperature sensor **210** may be placed in contact with housing **112** of implantable stimulation device **110**. Housing **112** is preferably made of metal. As housing **112** is in good thermal contact with the tissues surrounding the housing and also with temperature sensor **210**, and because metal is a good conductor of heat, temperature sensor **210** can accurately measure the temperature of the body at the location where implantable stimulation device **110** has been implanted. Preferably implantable stimulation device **110** is implanted in the subclavian pocket and thus temperature sensor **210** measures the temperature of the body in the subclavian pocket. This temperature will vary based on such factors as external temperature and activity of the subject.

PPG Sensor **211** comprises a photoplethysmography sensor which may be used to measure oxygen saturation in the tissues adjacent the housing **112**. PPG Sensor **211** comprises a number of light sources of different wavelengths and a light detector. The light detector detects light from the light sources which is reflected back from the tissues next to PPG sensor **211**. Preferably implantable stimulation device **110** is implanted in the subclavian pocket and thus PPG sensor **210** may be used to measure the oxygen saturation level in the tissues of the subclavian pocket using pulse oximetry techniques as will be described in more detail with respect to FIGS. 7B-C. The oxygen saturation level in the tissues of the subclavian pocket as measured by PPG sensor **211** can be used as a measure of arterial oxygen saturation.

As further shown in FIG. 2, implantable stimulation device **110** comprises an impedance measuring circuit **213** which is enabled by host controller **260** via a control signal **214**. Certain applications for an impedance measuring circuit **213** include, but are not limited to, lead impedance surveillance during the acute and chronic phases for proper lead positioning or dislodgment; detecting operable electrodes and automatically switching to an operable pair if dislodgment occurs; measuring respiration or minute ventilation; measuring thoracic impedance for determining shock thresholds; detecting when the device has been implanted; measuring stroke volume; and detecting the opening of the valves, etc. Impedance measuring circuit **213** is advantageously coupled to the switch bank **274** so that any desired electrode may be used.

Host controller **260** is also coupled to a memory **294** by a suitable data/address bus **296**. Memory **294** stores the pro-

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grammable operating parameters used by the host controller **260** in order to customize the operation of implantable stimulation device **110** to suit the needs of a particular patient. Such operating parameters define, for example, pacing pulse amplitude, pulse duration, electrode polarity, rate, sensitivity, automatic features, arrhythmia detection criteria, pacing mode, and the amplitude, waveshape and vector of each shocking pulse to be delivered to the patient's heart **100** within each respective tier of therapy. A feature of implantable stimulation device **110** is the ability to receive and store a relatively large amount of data (e.g., from data acquisition unit **290**), which data may then be used for subsequent analysis to guide the programming of implantable stimulation device **110**.

Advantageously, the operating parameters of the implantable device **110** may be non-invasively programmed into the memory **294** through a telemetry circuit **201** in telemetric communication with an external programmer **202**, such as a, transtelephonic transceiver, or a diagnostic system analyzer. The telemetry circuit **201** is activated by the host controller by a control signal **206**. The telemetry circuit **201** advantageously allows intracardiac electrograms, blood-glucose concentration results, oxygen saturation information, temperature data, hematocrit information, stroke volume, heart-rate, other measured physiological variable and status information relating to the operation of the implantable stimulation device **110** (as contained in the host controller **260** or memory **294**) to be sent to an external device such as programmer **202**, reader **203**, or portable device **204** through an established communication link **205**. Typically the communication link can only operate between telemetry circuit **201** and one of programmer **202**, reader **203**, or portable device **204** at any one time. A "handshake" signal sent from the external device may be used to identify the particular device with which the telemetry circuit **201** is in communication thereby defining what operations may be performed by the device. For example, programming of implantable stimulation device **110** will preferably only be permitted by programmer **202** under the control of a physician. xxx

Implantable stimulation device **110** further includes initiation circuit **235**. Initiation circuit **235** may comprise magnet detection circuitry. Initiation circuit **235** is coupled to host controller **260** by connection **236** and/or to telemetry circuit **201** by connection **234**. The purpose of the initiation circuit is to detect an initiation signal from outside the patient. For example, a magnet placed over the cardiac implantable stimulation device **110** may be used as the initiation signal, which magnet may be used by a clinician to perform various test functions of the cardiac implantable stimulation device **110** and/or to signal host controller **260** that an external programmer **202** is in place to receive or transmit data to host controller **260** through the telemetry circuit **201**. For examples of such devices, see U.S. Pat. No. 4,809,697, entitled "Interactive Programming and Diagnostic System for use with Implantable Pacemaker" (Causey, III. et al.); U.S. Pat. No. 4,944,299, entitled "High Speed Digital Telemetry System for Implantable Device" (Silvian); and U.S. Pat. No. 6,275,734, entitled "Efficient Generation of Sensing Signals in an Implantable Medical Device such as a Pacemaker or ICD" (note: this relates to transfer of EGM data) (McClure et al.), which patents are hereby incorporated herein by reference.

In an embodiment of the invention, a blood-glucose analysis unit **268** of host controller **260** processes signals representative of heart-rate, stroke volume, arterial oxygen saturation, hematocrit, blood flow, blood pressure, venous oxygen saturation and temperature, or sub-combinations thereof. Oxymetry processing unit **264** calculates oxygen saturation and

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hematocrit information from the outputs of an oxymeter **124** (See FIG. 1). PPG processing unit calculates oxygen saturation from the output of the PPG sensor **211**. Cardiac output processing unit **263** determines cardiac output from measures of stroke volume and heart-rate using electrocardiographic and bioimpedance data. Blood-glucose analysis unit **268** calculates the current blood-glucose concentration within the bloodstream of the patient from the oxymetric, temperature, and electrocardiographic data in combination with parameters stored in memory **294**. The operation of blood-glucose analysis unit **268** is described in detail below with reference to FIG. 5. In an embodiment of the invention host controller **260** also includes: a hypoglycemia detection unit **267** for controlling the detection of episodes of hypoglycemia based on the EGM; and a hyperglycemia detection unit **269** for controlling the detection of episodes of hyperglycemia based on the EGM. The output of hypoglycemia detection unit **267** and hyperglycemia detection unit **267** may be used to confirm, enhance and/or trigger the analysis of blood-glucose analysis unit **268**.

If an insulin pump **207** is provided, blood-glucose analysis unit **268** transmits control signals to insulin pump **207** for adjusting the amount of insulin delivered to the patient in response to the current blood-glucose concentration. Information regarding implantable insulin pumps may be found in U.S. Pat. No. 4,731,051 to Fischell and in U.S. Pat. No. 4,947,845 to Davis, both of which are incorporated by reference herein. The insulin pumps discussed therein, or other suitable insulin pumps, are modified to permit receipt of control signals from blood-glucose analysis unit **268**. Blood-glucose analysis unit **268** can likewise be used to control other implantable therapeutic devices which can be used to affect blood-glucose concentration. For example, it has been suggested that stimulation of the autonomic nerves innervating the pancreas may be used to control insulin secretion. This stimulation could be achieved using properly placed electrodes connected to terminals of implantable stimulation device **110**. The stimulation may be adjusted in response to control signals from blood-glucose analysis unit **268** thereby affecting the amount of insulin secreted by the pancreas in response to the calculated blood-glucose level.

Implantable stimulation device **110** additionally includes a power source such as a battery **214** which provides operating power to all the circuits of implantable stimulation device **110**. For implantable stimulation device **110**, which employs shocking therapy, battery **214** should be capable of operating at low current drains for long periods of time and also be capable of providing high-current pulses (for charging capacitor **212**) when the patient requires a shock pulse. Battery **214** preferably has a predictable discharge characteristic so that elective replacement time can be detected. Accordingly, implantable stimulation device **110** can employ lithium/silver vanadium oxide batteries.

2. Programmer

FIG. 3 illustrates components of a programmer **202** for use in programming an implantable medical device capable of determining blood-glucose concentration utilizing the metabolic oxygen concentration method and EGM analysis in accordance with specific embodiments of the present invention. Programmer **202** permits a physician or other user to program the operation of the implantable stimulation device **110** and to retrieve and display information received from the implantable stimulation device **110** such as stroke volume, heart-rate, oxymetry data, PPG data, blood-glucose concentration data, measured physiological variables data, EGM data and device diagnostic data. Additionally, programmer **202** may receive and display ECG data from separate external

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ECG leads that may be attached to the patient. Programmer 202 may also be capable of processing and analyzing data received from the implantable stimulation device 110 and from the ECG leads 332 to, for example, render preliminary diagnosis of medical conditions of the patient or the operations of the implantable stimulation device 110.

Operations of programmer 202 are controlled by a CPU 302, which may be a generally programmable microprocessor or microcontroller or may be a dedicated processing device such as an application specific integrated circuit (ASIC) or the like. Software instructions to be performed by the CPU are accessed via an internal bus 304 from a read only memory (ROM) 306 and random access memory 330. Additional software may be accessed from a hard drive 308, floppy drive 310, and CD ROM 312, or other suitable permanent mass storage device. Depending upon the specific implementation, a basic input output system (BIOS) is retrieved from the ROM by CPU at power up. Based upon instructions provided in the BIOS, the CPU "boots up" the overall system in accordance with well-established computer processing techniques.

Once operating, the CPU displays a menu of programming options to the user via an LCD display 314 or other suitable computer display device. To this end, the CPU may, for example, display a menu of specific programming parameters of the implantable stimulation device 110 to be programmed or may display a menu of types of diagnostic data to be retrieved and displayed. In response thereto, the physician enters various commands via either a touch screen 316 overlaid on the LCD display 314 or through a standard keyboard 318 supplemented by additional custom keys 320, such as an emergency VVI (EVVI) key. The EVVI key sets the implantable stimulation device 110 to a safe VVI mode with high pacing outputs. This ensures life sustaining pacing operation in nearly all situations but by no means is it desirable to leave the implantable device in the EVVI mode at all times.

Typically, the physician initially controls programmer 202 to retrieve data stored within the implanted medical device and to also retrieve ECG data from ECG leads 332, if any, coupled to the patient. To this end, CPU 302 transmits appropriate signals to a telemetry subsystem 322, which provides components for directly interfacing with the implantable stimulation device 110, the blood-glucose monitor 329 and the ECG leads 332. Telemetry subsystem 322 includes its own separate CPU 324 for coordinating the operations of the telemetry subsystem. Main CPU 302 of programmer 202 communicates with telemetry subsystem CPU 324 via internal bus 304. Telemetry subsystem 322 includes a telemetry circuit 326 connected to a telemetry wand 328, which, in turn, receives and transmits signals electromagnetically from a telemetry circuit 201 of a implantable stimulation device 110. Telemetry wand 328 is placed over the chest of the patient near the implantable stimulation device 110 to permit reliable transmission of data between the telemetry wand and the implantable stimulation device 110. Typically, at the beginning of the programming session, programmer 202 controls the implantable stimulation device 110 via appropriate signals generated by telemetry wand 328 to output all previously recorded patient and device diagnostic information. Patient diagnostic information includes, for example, stroke volume, heart-rate, oxymetry data, PPG data, blood-glucose concentration data, measured physiological variables data, recorded EGM data and statistical patient data such as the percentage of paced versus sensed heartbeats. Device diagnostic data includes, for example, information representative of the operation of the implantable stimulation device 110 such as lead impedances, battery voltages, battery recommended

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replacement time (RRT) information and the like. Data retrieved from the implantable stimulation device 110 is stored by programmer 202 either within a random access memory (RAM) 330, hard drive 308 or within a floppy diskette placed within floppy drive 310. Additionally, or in the alternative, data may be permanently or semi-permanently stored within a compact disk (CD) or other digital media disk, if the overall system is configured with a drive for recording data onto digital media disks, such as a write once read many (WORM) drive.

Once all patient and device diagnostic data previously stored within the implantable stimulation device 110 is transferred to programmer 202, the implantable stimulation device 110 may be further controlled to transmit additional data in real time as it is measured by the implantable stimulation device 110, such as additional stroke volume, heart-rate, oxymetry data, PPG data, blood-glucose concentration data, measured physiological variables data, EGM data, lead impedance data, and the like. Telemetry subsystem 322 may include input/output circuit 346 for communicating with external blood-glucose monitor 329.

Telemetry subsystem 322 is connected to blood-glucose monitor 329 by input/output circuit 346. Blood-glucose monitor 329 is a conventional external blood-glucose monitor which monitors the concentration of glucose in samples of the patient's blood using standard methods such as the hexokinase method. Additionally, telemetry subsystem 322 may receive ECG signals from ECG leads 332 via an ECG circuit 334. As with data retrieved from the implantable stimulation device 110, signals received from the ECG leads 332 and blood-glucose monitor 329 are stored within one or more of the storage devices of the external programmer. Typically, ECG leads output analog electrical signals representative of the ECG. Accordingly, ECG circuit 334 includes analog to digital conversion circuitry for converting the signals to digital data appropriate for further processing within programmer. Depending upon the implementation, the ECG circuit may be configured to convert the analog signals into event-record data for ease of processing along with the event-record data retrieved from the implantable stimulation device 110. Typically, signals received from the ECG leads 332 and blood-glucose monitor 329 are received and processed in real time.

Thus, programmer 202 receives data both from the implantable stimulation device 110 and from the external ECG leads and blood-glucose monitor. Data retrieved from the implantable stimulation device 110 includes parameters representative of the current programming state of the implantable stimulation device 110. Under the control of the physician, programmer 202 displays the current programming parameters and permits the physician to reprogram the parameters. To this end, the physician enters appropriate commands via any of the aforementioned input devices and, under control of CPU 302, the programming commands are converted to specific programming parameters for transmission to the implantable stimulation device 110 via telemetry wand 328 to thereby reprogram the implantable stimulation device 110. Prior to reprogramming specific parameters, the physician may control the programmer 202 to display any or all of the data retrieved from the implantable stimulation device 110 or from the ECG leads, including displays of ECGs, EGMs, and statistical patient information. Any or all of the information displayed by programmer may also be printed using a printer 336.

CPU 302 includes a blood-glucose concentration calibration unit 350 for generating patient-specific parameters for transmission to implantable stimulation device 110. Data for

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the operation of the blood-glucose concentration calibration unit 350 is derived from measurements of stroke volume, heart-rate, oxymetry data and other measured physiological variables transmitted from implantable device 110 via telemetry wand 328 in addition to the data recorded by blood-glucose monitor 329. The operation of blood-glucose concentration calibration unit 350 is described in detail below primarily with reference to FIG. 5.

Programmer 202 also includes a network interface card ("NIC") 360 to permit transmission of data to and from other computer systems via a router 362 and wide area network ("WAN") 364. Alternatively, programmer 202 might include a modem for communication via the public switched telephone network (PSTN). Depending upon the implementation, a modem may be connected directly to internal bus 304 may be connected to the internal bus via either a parallel port 340 or a serial port 342. Other peripheral devices (such as the blood-glucose monitor) may be connected to the programmer 202 via parallel port 340 or a serial port 342 as well. Although one of each is shown, a plurality of input output (IO) ports might be provided.

A speaker 344 is included for providing audible tones to the user, such as a warning beep in the event improper input is provided by the physician. Telemetry subsystem 322 additionally includes an input/output circuit 346 which can control the transmission of analog output signals, such as EGM signals output to an ECG machine or chart recorder.

With the programmer configured as shown, a physician or other user operating the programmer 202 is capable of retrieving, processing and displaying a wide range of information received from the ECG leads or from the implantable stimulation device 110 and to reprogram the implantable stimulation device 110 if desired. The descriptions provided herein with respect to FIG. 3 are intended merely to provide an overview of the operation of programmer and are not intended to describe in detail every feature of the hardware and software of the device and are not intended to provide an exhaustive list of the functions performed by the device.

3. Metabolic Oxygen Conformation Method for Blood-Glucose Analysis

The metabolic oxygen conformation method allows for calculation of blood-glucose concentration without the use of amperometric enzymatic biosensors. Blood-glucose concentration may be monitored by monitoring physiological variables that relate to glucose metabolism and deriving parameters that relate those variables to the concentration of glucose in the blood. The metabolism of glucose is the primary use of oxygen in the human body. Thus, in the metabolic oxygen conformation method, oxygen metabolism is used as a proxy for glucose metabolism. The following conceptual equation indicates the relationship between blood-glucose concentration and physiological variables related to oxygen metabolism:

$$G=F(\text{oxygen consumption, blood flow, oxygen concentration, temperature})$$

"G" represents the concentration of glucose in the blood and "F" is a relationship function between a set of interdependent and correlated metabolic variables related to oxygen metabolism (as a proxy for glucose metabolism). The parameters of the relationship function "F" may be determined by using multivariate statistical techniques to compare the conventionally-measured blood-glucose concentrations to the measured metabolic variables over a range of different blood-glucose concentrations in a specific patient or in clusters of patients within a population. In one embodiment of the invention, the relationship function "F" is determined using regression

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analysis. When determining the relationship function between the measured variables and the blood-glucose concentration, linear relationships are preferred because they are simple to calculate and may provide an adequate equation for deriving the blood-glucose concentration of the patient. However, other mathematical relationships can instead be employed, including nonlinear equations.

Different combinations of variables may be monitored in order to create an accurate set of parameters to determine blood-glucose concentration in accordance with the conceptual equation of the metabolic oxygen conformation method. For example, oxygen consumption can be calculated by the Fick formula: oxygen consumption=cardiac output*(arterial oxygen concentration-venous oxygen concentration). Cardiac output can be calculated by stroke volume*heart-rate. Stroke volume may be determined e.g. by analysis of the time-varying impedance between an intracardiac electrode and the housing 112 of implantable stimulation device 110. Blood flow may be measured directly, or may be inferred from cardiac output (or cardiac output in combination with blood pressure). Thus, rather than using oxygen consumption as a variable, related variables can be used instead, namely: stroke volume, heart-rate, venous oxygen concentration, and arterial oxygen concentration. Likewise, rather than using venous oxygen concentration as a variable in the regression analysis, its sub-variables, venous oxygen saturation and hematocrit may be used instead. Temperature can be measured in the core and in peripheral tissues and will vary depending on activity levels and blood flow distributions. Referring again to the conceptual equation and making substitutions with the measured variables:

$$G=F(\text{oxygen consumption, blood flow, oxygen concentration, temperature})$$

$$\text{Oxygen consumption}=f(\text{stroke volume, heart rate, venous oxygen concentration, arterial oxygen concentration})$$

$$\text{Tissue blood flow}=f(\text{stroke volume, heart rate, blood pressure})$$

$$\text{Tissue oxygen concentration}=f(\text{venous oxygen concentration, arterial oxygen concentration, blood flow})$$

$$\text{Venous oxygen concentration}=f(\text{hematocrit, venous oxygen saturation})$$

$$\text{Arterial oxygen concentration}=f(\text{hematocrit, arterial oxygen saturation})$$

$$\text{Thus, } G=F(\text{stroke volume, heart-rate, hematocrit, venous oxygen saturation, arterial oxygen saturation, blood pressure, core temperature, peripheral temperature}).$$

Other variables that relate to glucose or oxygen metabolism may be added if desired to improve the accuracy of the blood-glucose concentration determination, for example, blood pressure measured in the core and peripheral tissues, blood flow measured by a discrete flow meter (such as a Doppler flow meter). Blood pressure may be a useful variable in order to deal with varying blood flow distributions in various body conditions. For example, vasodilation usually leads to high peripheral blood flow, and lower blood pressure for the same cardiac output. Whereas vasoconstriction leads to low peripheral blood flow and higher blood pressure for the same cardiac output. Hematocrit and venous and arterial oxygen concentration may be measured by an oxymeter or PPG sensor as described with reference to FIGS. 7A-C below.

In principle, regression analysis models the relationship between one or more response variables (also called dependent variables), and the predictors (also called independent variables). Simple linear regression and multiple linear regression are related statistical methods for modeling the relationship between two or more random variables using a linear equation. Simple linear regression refers to a regression on two variables while multiple regression refers to a regression on more than two variables. Regression analysis can be used to determine the parameters of the relationship between the variables of the conceptual equation of the Metabolic Oxygen Conformation Method. In order to perform the regression analysis, data should be collected regarding the variables over a wide range of conditions as will be described with respect to FIGS. 4 and 5. During the regression analysis of the measured variables compared to actual blood-glucose concentration the measured variables necessary for an accurate blood-glucose concentration determination may be selected and others may be found unnecessary and dropped from later calculations. Thus, regression analysis may show that measurement of certain variables is not required in some individuals or clusters of individuals but is required in other individuals and clusters of individuals. The regression analysis generates parameters which specify which variables are required to be measured and the relationship of those variables to the subjects' blood-glucose concentration. Depending on the individual or cluster of individuals and the accuracy with which glucose concentration is required regression analysis of the data may demonstrate the following combinations of physiological metrics, for example, to be sufficient to calculate glucose concentration: venous oxygen saturation; venous oxygen saturation and temperature; venous oxygen saturation and hematocrit; venous oxygen saturation, temperature and heart-rate; venous oxygen saturation and blood pressure; venous oxygen saturation, blood pressure and heart-rate; hematocrit and temperature; and hematocrit, blood pressure and heart rate.

In FIGS. 4 and 5, flow charts are provided illustrating the operation and novel features of various exemplary embodiments of the invention. In the flow charts, various algorithmic steps are summarized in individual "blocks". Such blocks describe specific actions or decisions to be made or carried out as the algorithm proceeds. Where a microcontroller (or equivalent) is employed, the flow charts presented herein provide the basis for a "control program" that may be used by such a microcontroller (or equivalent) to effectuate the desired control of the device. Those skilled in the art may readily write such a control program based on the flow charts and other descriptions presented herein.

FIG. 4 is a flowchart illustrating one embodiment of a calibration technique for use in determining patient-specific parameters for subsequent use by the blood-glucose analysis unit 268 of FIG. 2 when performing the steps of FIG. 5. FIG. 4 illustrates steps performed by the programmer 202 of FIG. 3 and by the implantable stimulation device 110 of FIGS. 1 and 2 with steps performed by the programmer 202 shown on the left and steps performed by the implantable stimulation device 110 shown on the right. Initially, at step 402, upon input of appropriate activation commands by a physician or clinician operating the programmer 202, the blood-glucose calibration unit 350 initiates the calibration procedure and transmits a signal to the implantable stimulation device 110 for controlling the blood-glucose analysis unit 268 of the implantable stimulation device 110 to enter a calibration mode, at step 404. In the calibration mode, the blood-glucose analysis unit receives heart-rate, stroke volume, oximetry values, PPG values, temperature measurements and other

physiological variables from sensors and electrocardiographic signals, at step 406, but does not calculate blood-glucose concentration. (Blood-glucose analysis unit 268 does not calculate blood-glucose concentration because it does not yet have the patient-specific parameters to calculate the blood-glucose concentration). Rather, at step 408, the implantable stimulation device simply transmits the measured variables 409 to programmer 202. Steps 406 and 408 are repeated in a loop until a completion signal is ultimately received.

Meanwhile, at step 410, blood-glucose concentration calibration unit 350 of the programmer 202 inputs blood-glucose concentrations derived from an external blood-glucose concentration monitor 329 while the physician delivers glucose to the patient either orally or intravenously for the purposes of raising the blood-glucose concentration at step 407. Alternatively, if the patient is an insulin-dependent diabetic, the physician merely withholds insulin that would otherwise be provided to thereby allow the blood-glucose concentration to rise. The blood-glucose concentration measured at step 410 may be received automatically from an external blood-glucose concentration monitor 329 that is directly coupled to programmer 202 or may be input manually by the physician based on information provided by the external blood-glucose concentration monitor. Any of a variety of commercially available external blood-glucose concentration monitors may be employed. Preferably, an external blood-glucose concentration monitor 329 is employed that is capable of substantially continuously monitoring and updating the blood-glucose concentration such that data can be input substantially continuously at step 410 to provide a precise record of blood-glucose concentration as a function of measured electrocardiographic data, oximetry values and other physiological values. Alternatively, the blood-glucose concentration may be calculated and input periodically, such as once every 10 to 15 minutes. In any case, the blood-glucose concentrations provided by the external blood-glucose concentration monitor 329 are recorded in the memory of programmer 202 for subsequent use. Electrocardiographic values, oximetry values and other physiological variables 409 from the implantable stimulation device 110 are received and stored at step 411. The blood-glucose concentration for the patient is allowed to rise until it exceeds 300 mg/dL. When the blood-glucose concentration exceeds 300 mg/dL, at step 412, programmer 202 moves on to step 413.

Beginning at step 413, the physician delivers insulin to the patient at step 424 to cause the blood-glucose concentration to decrease while programmer 202 continues to receive and store the blood-glucose concentration for the patient derived from the external monitor and continues to receive and store, at step 414, cardiac output, oximetry values and other physiological variables 409 measured by the implantable stimulation device 110. The patient's blood-glucose concentration is allowed to decrease until it falls below 40 mg/dL at step 415. When the patient blood-glucose concentration is below 40 mg/dL the data collection process is complete and a completion signal 426 is transmitted to the implantable stimulation device 110 at step 416. Upon receipt of the completion signal 426 at step 417, the implantable stimulation device 110 may suspend detection of cardiac output, oximetry values and other physiological variables 409.

The patient-specific parameters 419 of the relationship function are then calculated by programmer 202 at step 418 using the metabolic oxygen conformation method. In accordance with one embodiment of the metabolic oxygen conformation method, programmer 202 records data that provides the cardiac output, oximetry values and other physiological

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variables 409, for each input blood-glucose concentration throughout the range of 40 to 300 mg/dl during steps 410 to 416. At step 418, the blood-glucose concentration calibration unit 350 uses the metabolic oxygen conformation method to automatically determine a set of parameters that relate a selected group of the recorded oxymetric, electrocardiographic and physiological variables 409 to the actual recorded patient blood-glucose concentrations. In one embodiment of the invention, the parameters of the relationship function "F" are determined by using otherwise conventional regression analysis.

In another example, rather than fitting the data to a predetermined mathematical relationship, programmer 202 instead generates a lookup table relating cardiac output, oximetry values and other physiological variables 409 to patient blood-glucose concentration. The lookup table may be generated by interpolating, if desired, between individual data values recorded during steps 402-416. The lookup table is then transmitted to the implantable stimulation device 110 so the implantable stimulation device 110 can look up a value for the blood-glucose concentration for each combination of cardiac output and oximetry values. Although the use of a lookup table is certainly feasible, it requires more data to be stored within the implantable stimulation device 110. As can be appreciated a wide range of techniques may be employed for mathematically relating the cardiac output, oximetry values and other physiological variables 409 to the measured blood-glucose concentration and no attempt is made herein to describe all possible techniques.

After the patient specific parameters of the relationship function have been calculated at step 418, they are transmitted to implantable stimulation device 110 at step 418. Implantable stimulation device 110 receives and stores the patient-specific parameters at step 422. Thereafter, implantable stimulation device 110 begins monitoring blood-glucose concentration using the techniques described with respect to FIG. 5. Although not shown, the programmer 202 can also input control parameters provided by the physician for transmission to the implantable stimulation device 110, at step 416, for use in controlling the implantable stimulation device 110 or the implanted drug pump or other therapeutic device based on patient blood-glucose concentration. For example, the control parameters may specify an optimal blood-glucose concentration so that the implantable stimulation device 110 can then control the drug pump 207 to adjust the amount of insulin delivered to the patient to achieve the optimal blood-glucose concentration. The control parameters may also specify the specific upper and lower bounds used for generating warning signals.

4. Method for Enhanced Blood-Glucose Analysis Using Metabolic Oxygen Conformation and EGM

In accordance with specific embodiments of the present invention the glucose concentration analysis made using the metabolic oxygen conformation method is enhanced, triggered, or confirmed by additional analysis of EGM data. As will be discussed in more detail below, with reference to FIGS. 8-15, the metric of blood-glucose derived from the analysis of the EGM may be either quantitative (e.g. a blood-glucose concentration value) or qualitative (e.g. is hypoglycemia, hyperglycemia or normoglycemia present or absent) depending upon the methodology used. Analysis of EGM data can thus be used to determine the onset, existence and/or extent of hypoglycemia, normoglycemia and hyperglycemia.

Referring to FIG. 2, hypoglycemia detection unit 267 and hyperglycemia detection unit 269 of host controller 260 analyze EGM data and determine the presence, absence and/or extent of hypoglycemia, normoglycemia and hyperglycemia.

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This blood-glucose concentration analysis methodology is independent of the metabolic oxygen conformation method and thus may be used to trigger, enhance or confirm the metabolic oxygen conformation analysis. The results of EGM analysis by hypoglycemia detection unit 267 and hyperglycemia detection unit 269 are used in conjunction with blood-glucose analysis unit 268. In one embodiment, if the metabolic oxygen conformation method yields a first metric of blood-glucose concentration indicative of hypoglycemia or hyperglycemia, the parallel analysis of EGM data is triggered. If the EGM analysis yields a second metric of blood-glucose concentration also indicative of hypoglycemia or hyperglycemia then the confidence in the accuracy of the first metric is enhanced. Thus, utilizing EGM analysis in addition to the metabolic oxygen conformation method yields an enhanced metric of blood-glucose concentration where the metric is enhanced in terms of accuracy, quality, reliability and/or confidence. The enhanced metric may be used, for example to reduce the incidence of false warnings of hypoglycemia or hyperglycemia.

In specific embodiments of the present invention, metrics of blood-glucose concentration derived from different sensors are combined by blood-glucose analysis unit 268 of host controller 260 to generate an enhanced metric of blood-glucose concentration. Data, information, or sensor fusion is the integration of data from disparate sources. If one blood-glucose concentration metric is trusted blindly over the other, the final enhanced metric may not be as accurate as it can be. The combination of two (or more) blood-glucose concentration metrics into a single enhanced metric of blood-glucose concentration can be achieved by blood-glucose analysis unit 268 of host controller 260 using one or more multi-sensor fusion algorithms. Multi-sensor fusion algorithms can be divided into four categories: estimation methods, classification methods, inference methods and artificial methods. Estimation methods include different statistical methods like weighted averaging, least squares and Kalman filtering. Classification methods include various clustering methods and inference methods include Bayesian inference with extensions. Artificial intelligence methods include neural networks and fuzzy logic. The multi-sensor fusion algorithm used by blood-glucose analysis unit 268 of host controller 260 may also take into account blood-glucose concentration metric history stored in memory 294 and/or a model of blood-glucose concentration change over time.

In the real world all measurements have imprecisions that create a range of uncertainty for that measurement. Thus an experimental measurement results in a best estimate and a range of values. Conventionally, when comparing two different measurements, they can be said to agree if the ranges share common values, i.e. their uncertainty ranges overlap. In embodiments of the present invention, uncertainty ranges may be determined with respect to the metrics of blood-glucose concentration derived from the metabolic oxygen conformation method and the EGM analysis method. In specific embodiments of the present invention, the implantable device can thus determine whether the metrics are in agreement by comparing the uncertainty ranges for each metric to determine whether particular measurements overlap. The implantable device may also determine the magnitude of any discrepancy between the measurements. The discrepancy can be used as an indicator of the accuracy of the measurement. The accuracy, agreement and/or discrepancy of the two metrics of blood-glucose concentration may be used to generate the enhanced metric of blood-glucose concentration. In some embodiments, the measurements may be discarded and new measurement acquired if the measurements do not agree. In

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some embodiments, if the measurements are in agreement they may be combined using weighted averages (or other sensor fusion algorithms) to generate the enhanced metric of blood-glucose concentration.

Referring now to FIG. 5A, the operation of blood-glucose analysis unit 268 of FIG. 2 will be described. Initially, at step 422, the blood-glucose analysis unit receives and stores a set of parameters relating patient measured physiological variables to blood-glucose concentration. The parameters are preferably generated in advance using the method of FIG. 4, and then transmitted to the implantable stimulation device 110 by programmer 202 for storage in memory 294. The parameters are derived in advance using the metabolic oxygen conformation method. Particular parameters are calibrated for a user or cluster of users using regression analysis comparing conventionally-measured blood-glucose concentration to internally-measured physiological variables. One method of calibrating the parameters in accordance with the metabolic oxygen conformation method is described with respect to FIG. 4. The parameters are saved in memory 294 of implantable stimulation device 110. The implantable stimulation device 110 can thereafter continuously monitor blood-glucose concentration based on the measured oxymetric, electrocardiographic and other measured physiological variables and the stored patient-specific parameters.

At step 504, the implantable stimulation device 110 measures the physiological variables used for blood-glucose concentration analysis. These may include, by way of example, stroke volume, heart-rate, hematocrit, peripheral temperature, core temperature, venous oxygen saturation, arterial oxygen saturation, temperature, blood flow and blood pressure. The measured variables may, if desired or necessary be stored in memory 294 of implantable stimulation device 110. At step 506, blood-glucose analysis unit 268 of host controller 260 calculates the current blood-glucose concentration in the blood of the patient based on the physiological variables measured in step 504 and the patient-specific parameters stored in step 422. This first metric of blood-glucose concentration is then stored at step 507, and compared at step 508 against both an upper threshold and a lower threshold to ensure that the blood-glucose concentration is within acceptable bounds. In one example, the upper threshold is 120 mg/dl and the lower threshold is 60 mg/dl. The upper and lower threshold values are preprogrammed within the implantable stimulation device 110 and may be specified, for example, by a physician using programmer 202.

If the blood-glucose concentration is found to be outside the acceptable bounds at step 509, hypoglycemia detection unit 267 and hyperglycemia detection unit 269 are triggered to analyze EGM data at 510 and generate a second metric of blood-glucose concentration. If the second metric of blood-glucose concentration is also indicative of hypoglycemia or hyperglycemia then hypoglycemia or hyperglycemia is confirmed at step 511 and a warning signal is generated at step 512 to alert the patient. If hypoglycemia or hyperglycemia is not confirmed at step 511, no warning signal is generated at step 512 instead blood-glucose analysis unit 268 returns to step 504 for recalculation of blood-glucose concentration (or alternatively continues to step 514). A drug pump 207 or other therapeutic device can also be adjusted at step 512, as described in more detail below. The confirmation of hypoglycemia or hyperglycemia using the EGM analysis enhances the accuracy, quality, reliability and/or confidence in the blood-glucose concentration metric calculated using the metabolic oxygen conformation method.

At step 514, the rate of change of blood-glucose concentration is calculated and a time by which blood-glucose con-

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centration will be out of bounds is calculated based on the current blood-glucose concentration and the rate of change. If the blood-glucose concentration is predicted to be outside the acceptable bounds within 30 minutes at step 516, an early warning signal is generated at step 518. Analysis of EGM data to confirm the blood-glucose analysis may also be performed before generating the early warning signal if desired.

Preferably, a different warning signal is provided at step 512 when the blood-glucose concentration is too low than when it is too high. Additionally, the early warning signal of step 518 is preferably different than the warning signal of step 512. The early warning signal of step 518 is preferably initially of a lower intensity than the warning signal of step 512 and may be designed to increase in intensity as the predicted time within which blood-glucose concentration will be out of acceptable bounds reduces towards zero. Depending upon the configuration of the implantable stimulation device 110, the warning signal may be generated by causing the pacemaker to periodically vibrate inside the patient. Alternatively, the implantable stimulation device 110 may transmit a warning signal to an external warning device such as a bedside monitor or a portable device 204 carried with the patient, which displays and/or signals the warning to the patient.

If a warning signal is transmitted to an external warning device, the exact blood-glucose concentration is preferably also transmitted such that it can be displayed to the patient. Additionally, if the portable device 204 is provided with a wireless modem the warning signal may also be transmitted through a communications server and network, to other persons, such as the device manufacturer, a physician, clinician, nurse or caregiver. In the alternative, if an external warning device is provided, the current blood-glucose concentration may be transmitted periodically such that the patient is kept apprised of the current blood-glucose concentration. In other words, this information is not transmitted only when the blood-glucose concentration falls outside acceptable bounds but is transmitted periodically. In addition, since the blood-glucose concentration is recorded in memory at step 506, this information may be subsequently transmitted to the programmer 202 device for review by a physician during a subsequent office visit. Note that a wide range of other diagnostic information is routinely detected and recorded by the implantable stimulation device 110, such as heart-rate and the like. Accordingly, the blood-glucose concentration of the patient can be correlated with other diagnostic information to help the physician develop optimal therapies for the patient and to better tune the blood-glucose concentration determination and warning parameters.

At steps 513 and 520, if a drug pump or other therapeutic device to control blood-glucose concentration has been implanted in the patient, blood-glucose analysis unit 268 transmits appropriate control signals to the drug pump to adjust the amount of insulin provided to the patient or level of therapeutic intervention in response to the blood-glucose concentration and rate of change of blood-glucose concentration. For example, if the blood-glucose concentration has exceeded the upper bound, the drug pump is controlled to provide a greater amount of insulin to the patient. As with the generation of warning signals, control of the drug pump is not limited only to circumstances in which the blood-glucose concentration has exceeded the acceptable bounds. Rather, each newly calculated value for blood-glucose concentration may be used to control the drug pump 207 to maintain the blood-glucose concentration at a target concentration deemed by the physician to be optimal such as, for example, at 100 mg/dl.

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In one example, drug pump **207** is additionally controlled to modulate the blood-glucose concentration based upon the current activity level of the patient, for example, to increase the blood-glucose concentration whenever the patient is more active and to decrease it otherwise. The activity level may be inferred for example, from the rate of oxygen consumption determined from the stroke volume, heart-rate and oxymetry data. In another example, drug pump **207** is additionally controlled to deliver insulin based on the blood-glucose concentration and the rate of change of blood-glucose concentration. Additionally, other programmable features of the implantable stimulation device **110** may be adjusted based upon blood-glucose concentration and/or rate of change of blood-glucose concentration. As one example, if blood-glucose concentration is found to be particularly low, a base pacing rate may be reduced until the blood-glucose concentration returns to acceptable concentrations. Techniques for controlling delivery of therapy in response to hypoglycemia are set forth in the patent application of Kroll, incorporated by reference above. Information regarding implantable insulin pumps may be found in U.S. Pat. No. 4,731,051 to Fischell and in U.S. Pat. No. 4,947,845 to Davis both of which are incorporated herein by reference. A wide variety of techniques may be employed for controlling a drug pump **207** or for controlling various functions of the implantable stimulation device **110** and no attempt is made herein to describe all possible techniques.

The blood-glucose concentration calculated by blood-glucose analysis unit **268** is stored at step **507**. The stored blood-glucose concentration data is used in order to analyze the rate of change of blood-glucose concentration as part of the blood-glucose concentration trend analysis of step **514**. The stored blood-glucose concentration data may also be used to generate average blood-glucose concentration figures as a measure of the quality of blood-glucose regulation over time. In one example, average blood-glucose concentration may be calculated as a running average of its value over a certain time period (e.g., can be as long as three months). The HbA1c blood test is a measure of average blood-glucose concentration during the previous two to three months. The average blood-glucose concentration calculated by implantable device **110** over a two month to three month period can be used as a synthetic proxy for the HbA1c test and may be readily correlated to standard HbA1c test results. The average blood-glucose concentration may be calculated by implantable stimulation device **110** or implantable stimulation device **110** may generate and store daily blood-glucose concentration averages which can then be downloaded and averaged by programmer **202** or reader **203**, or portable device **204**. In this way, the overall effectiveness of blood-glucose concentration regulation can be monitored without requiring HbA1c blood tests.

Referring now to FIG. **5B**, the operation of an alternative embodiment of blood-glucose analysis unit **268** of FIG. **2** will be described. Initially, at step **422**, the blood-glucose analysis unit receives and stores a set of parameters relating patient measured physiological variables to blood-glucose concentration as in FIG. **5A**. At step **504**, the implantable stimulation device **110** measures the physiological variables used for blood-glucose concentration analysis. At step **506**, blood-glucose analysis unit **268** of host controller **260** calculates the current blood-glucose concentration in the blood of the patient based on the physiological variables measured in step **504** and the patient-specific parameters stored in step **422**. Next, at step **530**, EGM data is analyzed (as further described below) to determine a metric of blood-glucose concentration. Next at step **532**, the blood-glucose concentration determined

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by the blood-glucose analysis unit **268** is combined and/or compared with the results of the EGM utilizing one of the data/sensor fusion techniques described above to generate an enhanced blood-glucose concentration value. In a simple embodiment, a weighted average of the two metrics may be used as the enhanced metric of blood-glucose concentration. The enhanced blood-glucose concentration metric may be enhanced in terms of accuracy, quality, reliability and/or confidence. In some circumstances, where there is too much discrepancy between the blood-glucose concentration values determined using the different methodologies, the analysis may return to step **504** to measure the physiological variables again. The enhanced blood-glucose concentration metric is stored at step **507**.

At step **508** the enhanced blood-glucose concentration is compared with an upper threshold and a lower threshold to ensure that the blood-glucose concentration is within acceptable bounds. In one example, the upper threshold is 120 mg/dl and the lower threshold is 60 mg/dl. The upper and lower threshold values are preprogrammed within the implantable stimulation device **110** and may be specified, for example, by a physician using programmer **202**. If the blood-glucose concentration is found to be outside the acceptable bounds at step **509**, a warning signal is generated at step **512** to alert the patient. A drug pump **207** or other therapeutic device can also be adjusted at step **513**, as described in more detail below. At step **514**, the rate of change of blood-glucose concentration is calculated and a time by which blood-glucose concentration will be out of bounds is calculated based on the current blood-glucose concentration and the rate of change. If the blood-glucose concentration is predicted to be outside the acceptable bounds within 30 minutes at step **516**, an early warning signal is generated at step **518** and control signals are transmitted to a therapeutic device (if present) at step **520**.

The analysis of FIGS. **5A** and **5B** can be repeated at intervals to update the blood-glucose concentration measurement. For example, the measurement may be repeated once every minute, once every 15 minutes, or once every hour. Preferably, the interval between calculations of blood-glucose concentration is selected so as to maintain adequate control of blood-glucose concentration and programmed in advance by a physician using programmer **202**. The interval between blood-glucose concentration measurement updates may also vary depending upon the glucose concentration, the rate of change of glucose concentration, or the activity of the subject. For example, if the rate of change of glucose concentration is determined to be high at step **514**, the interval until the next update may be reduced compared to the normal update interval. Conversely, if the rate of change of glucose concentration is determined to be low at step **514**, the interval until the next update may be increased compared to the normal update interval. Likewise, if the blood-glucose concentration is found to be below a threshold, such as 70 mg/dl or above a threshold such as 110 mg/dl the interval until the next update may be reduced compared to the normal update interval. The reduced interval between updates thus allows for more accurate analysis of the current blood-glucose level during high risk periods, i.e. when blood-glucose is changing rapidly or the subject is close to hypoglycemia or hyperglycemia.

In the embodiment of FIG. **6**, the results of EGM analysis by hypoglycemia detection unit **267** and hyperglycemia detection unit **269** are used to trigger analysis using the metabolic oxygen conformation method by glucose concentration analysis unit **268**. Referring now to FIG. **6**, at step **600** EGM data is analyzed by hypoglycemia detection unit **267** and hyperglycemia detection unit **269**. If no hypoglycemia or hyperglycemia is detected at step **602** the system recycles to

step 600 to continue to monitor EGM data. If hypoglycemia or hyperglycemia is detected at step 602 then the system proceeds to step 603 in which blood-glucose analysis using the metabolic oxygen conformation method is triggered. Thereafter the blood-glucose analysis and resulting action are performed similarly to FIGS. 5A and 5B. After the completion of the analysis and any warning that results, the system returns to step 600 to monitor the EGM for indicators of hypoglycemia and hyperglycemia. The method of FIG. 6 allows for reduced time of use of the oxymetry and PPG sensors with commensurate power savings and also increased longevity of the sensors. The EGM analysis does not require operation of the oxymetry sensors. Moreover, in a cardiac stimulation device, EGM sensing and analysis is typically performed continuously. The oxymetry and PPG sensors may be powered down until analysis of the EGM indicates the possibility of hypoglycemia and hyperglycemia at which time the oxymetry and PPG sensors may be powered up to analyze the blood-glucose concentration.

Oxymetry and PPG Sensors

Oxymetry and PPG sensors may be used in some embodiments of the present invention to measure physiological properties related to oxygen metabolism for use in the metabolic oxygen conformation method. This section describes exemplary oxymetry and PPG sensors suitable for this purpose. Referring now to FIG. 7A, there is shown an exemplary oxymeter 124 suitable for use in an embodiment of the present invention. In accordance with embodiments of the present invention, blood-glucose concentration is calculated in part by measuring a proxy for glucose metabolism. Glucose metabolism is the primary use of oxygen in the human body. Hence, in the metabolic oxygen conformation method, oxygen consumption is used as a proxy for glucose metabolism. Oxygen consumption can be measured using a combination of implantable sensors. One way to analyze oxygen consumption is to measure the difference in the concentration of oxygen in the arterial blood and the venous blood and multiply by the cardiac output. Oxymeter 124 of FIG. 7A may be utilized to measure the concentration of oxygen in the blood utilizing a two step process: first determining blood-oxygen saturation; and second determining hematocrit. Blood-oxygen concentration is proportional to blood-oxygen saturation multiplied by hematocrit.

Blood-oxygen saturation is the relative amount of oxygenated hemoglobin in all of the hemoglobin present in the blood stream. This hemoglobin is packaged in biconcave discs of approximately 10 micrometers diameter which commonly occur with a density of approximately five million red blood cells per cubic millimeter. When radiant energy (e.g., light) is incident upon red blood cells, the red blood cells both scatter and transmit the incident radiant energy. The differential absorption by oxygenated and non-oxygenated hemoglobin of the radiant energy of particular wavelengths reflected by and transmitted through the red blood cells furnishes the basis for the oxygen saturation measurements.

An oxymeter uses light sources of two or more different centered wavelengths to obtain measures of blood-oxygen saturation by measuring the absorption and/or scattering of those wavelengths by oxyhemoglobin and reduced hemoglobin in the blood. The absorption and/or scattering is measured using a light sensor. The measured absorption and/or scattering data allows for the calculation of the relative concentration of reduced hemoglobin and oxyhemoglobin, and therefore blood-oxygen saturation levels, since the absorption and/or scattering relationships are known.

In addition to using the above described light sources and light sensors to measure levels of blood-oxygen saturation,

they can also be used to measure levels of hematocrit, which refers to the percentage of packed red blood cells in a volume of whole blood. Implanted optical sensors can also be used to measure levels of hematocrit, which refers to the percentage of packed red blood cells in a volume of whole blood. Various techniques are known for determining hematocrit based on scattered light. In one technique, a pair of spatially separated photo detectors can be used to detect reflected infra red (IR) light, e.g., of 805 nm. The intensity of the IR light detected by the photo detector that is nearer to the IR light source is referred to as IRnear, and the intensity of the IR light detected by the photo detector farther from the IR light source is referred to as IRfar. As described in article by Bornzin et al., entitled "Measuring Oxygen Saturation and Hematocrit Using a Fiberoptic Catheter", *IEEE/9th Annual Conf of the Eng. & Biol. Soc.* (1997), which is incorporated herein by reference, the ratio: $R = IR_{near}/IR_{far}$ is directly related to the level of hematocrit, but independent of oxygen saturation because 805 nm is an isobestic wavelength. Hematocrit can be measured with similar results using a single light detector, and two light sources, where one source is located closer to the light detector than the other (again producing IRnear and IRfar measurements). In another technique, light of about 500 nm and light of about 800 nm can be directed at a blood sample, and an algorithm can be used to calculate hematocrit based on the intensities of detected scattered light.

In accordance with a specific embodiment of the present invention, the implantable oxymeter 124 includes an implantable housing 704 including a window 706 through which light can pass to fall on red blood cells 700. The term window, as used herein, is intended to collectively encompass all portions of the housing through which light of interest can enter and exit the housing, even if such portions are separated from one another (e.g., by opaque portions). Included within the housing are three light sources 708, one far light source 710, a measurement light sensor 712 and a calibration light sensor 714. One of each of the light sources 708 transmits light at each of the wavelengths 670 nm, 705 nm, and 805 nm. Far light source 710 transmits light at the isobestic wavelength 805 nm. The intensity of the light transmitted by each light source is controlled by a corresponding drive signal 707, 709 that drive the light sources 708 and far light source 710. The drive signal may be different for each of the three wavelengths emitted by light sources 708. A portion of the light of each wavelength exits the housing through the window 706. The measurement light sensor 712 detects light of each wavelength scattered back into the housing through the window 706, and produces a measurement signal 714 that is indicative of the intensity of the light of each wavelength detected by the measurement light sensor. A portion of window 706 above calibration sensor 714 is provided with a reflective surface 720 to reflect some but not all of the light waves onto the calibration light sensor 714. The calibration light sensor detects a portion of the light of each wavelength that has not exited the housing and produces a calibration signal 716 that is indicative of the intensity of the light of the wavelength detected by the calibration light sensor 714, which is indicative of the intensity of the light transmitted by each light source.

In accordance with specific embodiments, a controller adjusts drive signals 707, 709 based on the calibration signal 716, to keep the intensity of the light transmitted by each light source substantially constant. In accordance with other embodiments of the present invention, a controller adjusts the measurement signal 714, based on the calibration signal, to compensate for changes in the intensity of the light transmitted by each light source 708, 710. In still other embodiments,

rather than adjusting signals, the oxymetry processing unit **264** (that uses the measurement signal for a diagnostic and/or therapeutic purpose) detects changes in the intensity of the light transmitted by each light source based on the calibration signal **714**, and takes into account the changes in intensity when using the measurement signal **714** for a diagnostic and/or therapeutic purpose. For example, the oxymetry processing unit **264** can take such changes in intensity into account by making appropriate adjustments to algorithms that are used to determine levels of blood-oxygen saturation and/or levels hematocrit based on the measurement signal.

ASIC **722** comprises a plurality of digital to analog converters and analog to digital converters for providing the drive signals **707**, **709** to drive the light sources **708** and far light source **710** and receive the measurement signal **714** and calibration signal **716**. ASIC **722** communicates a digital representation of the measurement signal **714** and calibration signal **716** for each of light sources **708** and far light source **710** to implantable stimulation device **110** via right atrial lead **120** and receives power from implantable stimulation device **110** via right atrial lead **120**. Lead **120** comprises one or more conductive wires to connect ASIC **722** to implantable stimulation device **110**.

More detailed descriptions of oxymeters suitable for use in embodiments of the present invention may be found in copending patent application U.S. Ser. No. 11/282,198 filed Nov. 17, 2005 entitled "Implantable Self Calibrating Optical Sensors" and invented by John W. Poore, which is incorporated herein by reference. Moreover, oxymeter as used herein is not to be limited to the particular oxymeter disclosed herein. Blood-oxygen concentration may be measured by several technologies. As used herein "oxymeter" should be interpreted to encompass any device or technology that can be used to determine oxygen concentration in the blood.

Referring again to FIG. 7A, housing **704** of oxymeter **124** is also shown to enclose temperature sensor **724**. Temperature sensor **724** may comprise any electronic device for measuring temperature. Suitable devices include, but are not limited to, thermopiles, thermistors, thermocouples. Thermopiles measure temperature by measuring IR radiation incident of the detector surface. Thus, if a thermopile is used as temperature sensor **724**, a window transparent to IR (not shown) should be provided to allow heat/IR radiation from the blood to fall on the surface of the detector. Thermistors and thermocouples may measure temperature by conduction. Such temperature measuring devices should therefore be placed in good thermal contact with the blood. As shown in FIG. 7A, temperature sensor **724** may be placed in contact with housing **704** of oxymeter **124**. Housing **704** is preferably made of metal. As housing **704** is in good thermal contact with the blood and with temperature sensor **724**, and because metal is a good conductor of heat, temperature sensor **724** can accurately measure the temperature of the blood. Although temperature sensor **724** is shown as part of oxymeter **124**, a separate temperature sensor device may be used.

Referring again to FIG. 1, in one embodiment of the present invention, oxymeter **124** can be designed for implantation in the right atrium **102** of a heart **100**. The right atrium of the heart receives deoxygenated blood from the body by way of the superior and inferior vena cava. The deoxygenated blood is pumped from the right atrium **102** to the right ventricle **104** and thence to lungs where it is re-oxygenated. Thus, measuring the concentration of oxygen in the blood in the right atrium **102** or right ventricle **104** reveals how much oxygen was used by the body since that blood was last pumped through the lungs. The right atrium is an ideal location for the oxymeter because in the right atrium all the

venous blood from the entire body is mixed. However, oxymeter **124** could be located in the inferior or superior vena cava instead of the right atrium although the results may not be quite so complete. In order to minimize the number of implantable devices, oxymeter **124** (not shown) is preferably built into implantable right atrial lead **120** which is already to be implanted into the right atrium. If desired or necessary a second oxymeter may be provided to monitor the arterial oxygen concentration in blood returning from the lungs via the pulmonary veins to the left atrium. In such case, an oxymeter as described above may be included in left atrial sensor **152**. An oxymeter, as described above, could also be mounted externally on the housing **112** of implantable stimulation device **110** to measure oxygen saturation of the blood perfusing the tissues surrounding the implantable stimulation device **110**.

Referring now to FIGS. 7B-C which illustrate a photoplethysmography ("PPG") sensor built into the housing **112** of implantable stimulation device **110**. FIG. 7B shows an embodiment of a PPG sensor **211** which can also be used to measure oxygen saturation. As shown in FIG. 7B, PPG sensor **211** comprises a light source **732**, which preferably comprises parallel and oppositely oriented red and infrared LEDs positioned such that light is directed into the overlying tissue, and a light detector **734**, preferably a photodiode, positioned such that it collects light reflected by the overlying tissue. The electronic circuitry associated with the light source and sensor is well known for external pulse oximeters, and is described in, e.g., U.S. Pat. No. 4,869,254 entitled, "Method And Apparatus For Calculating Arterial Oxygen Saturation" to Stone et al., and U.S. Pat. No. 5,078,136, entitled, "Method And Apparatus For Calculating Arterial Oxygen Saturation Based Plethysmographs Including Transients" to Stone et al. both of which are incorporated herein by reference. Alternate embodiments of the PPG sensor for oxygen saturation analysis may use more than two wavelengths, for example, as described with respect to the oxymeter of FIG. 7A. Alternatively, a single wavelength driven at two different current levels might be used, such as in the technique described in U.S. Pat. No. 4,815,469 entitled "Implantable Blood Oxygen Sensor And Method Of Use" to Cohen et al. which is incorporated herein by reference.

Returning to the embodiment of the combined vascular plethysmography and O₂ saturation sensor shown in FIG. 7B, the source **732** and detector **734** are placed in a well **740** and that is created when the monitor housing **112** is machined, formed, or cast. In the preferred embodiment well **740** is formed using the minimum volume necessary to contain its feed through connector and optical device. A light barrier **736** is positioned between the source and detector to ensure that no light passes directly between them. The source and the detector are physically positioned such that the amount of light received at the detector is maximized. In particular, they are angled toward each other such that the direction of greatest optical power and sensitivity are aligned. Furthermore, in the preferred embodiment the optical devices have inherent directionality to avoid the need for lenses or other focusing elements, though these are used in alternate embodiments. The remaining space in the well is filled with epoxy such that the surface of the monitor **20** is smooth and flat, thereby minimizing the risk of tissue trauma and infection. The optical source **26** and detector **28** are connected via feed-through connections **742** and **744** to PPG Processing Circuit **265** thus ensuring hermeticity.

The light source **732** and the light detector **734** are preferably placed on the side of the implantable stimulation device **110** that, following implantation faces the chest wall, and are

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configured such that light cannot pass directly from the source to the detector. Thus, the reflection configuration is preferably used when the plethysmography device is implemented in an implantable device. The placement on the side of the device that faces the chest wall maximizes the signal to noise ratio by 1) directing the signal toward the highly vascularized musculature, and 2) shielding the source and detector from ambient light that enters the body through the skin. Alternatively, at the risk of increasing susceptibility to ambient light, the light source **732** and the light detector **734** can be placed on the face of the device that faces the skin of the patient.

The light source **732** can transmit light of more than one wavelength. For example, in an embodiment of the present invention the light source **732** transmits light having a first wavelength and light having a second wavelength. More specifically, in one embodiment light source **362** outputs visible red light e.g., 660 nm wavelength and outputs an infrared or near infrared light signal e.g., 940 nm wavelength. In this embodiment, the light output from light source **732** is serially pulsed to produce an interleaved light stream that is detected by light detector **734**. The light stream consists of interleaved visible red light and infrared radiation. The interleaved signal stream is reflected from tissue of a patient and light is received by light detector **734**. As the light is reflected from tissue, some of the energy is absorbed by arterial and venous blood, tissue and the variable pulsations of arterial blood. Analog signals representative of the reflected light of the two wavelengths are converted to digital signals and transmitted to PPG processing unit **265** of host controller **260**. PPG processing unit **265** calculates blood oxygenation levels based on these signals. The blood oxygenation level in the tissues of the subclavian pocket adjacent the implantable stimulation device **110** may be used as a measure of arterial oxygen saturation. It is noted that the term "light" refers to both visible and non-visible light, with light being further defined, when necessary, by specific wavelengths (e.g., visible red or infrared). Additional details of implantable PPG devices suitable for use as a PPG sensor in embodiments of the present invention are disclosed in U.S. Pat. No. 6,491,639, entitled "Extravascular Hemodynamic Sensor" to Turcott, U.S. Pat. No. 6,731,967, entitled "Methods And Devices For Vascular Plethysmography Via Modulation Of Source Intensity" to Turcott, and U.S. Pat. No. 6,997,879, entitled "Methods And Devices For Reduction Of Motion-Induced Noise In Optical Vascular Plethysmography" to Turcott all of which are incorporated herein by reference.

Referring again to FIG. 7C a temperature sensor **210** is shown in contact with housing **112**. Temperature sensor **210** may comprise any electronic device for measuring temperature. Suitable devices include, but are not limited to, thermopiles, thermistors, thermocouples. Temperature sensor **724** can accurately measure the temperature of the body in the subclavian pocket as a measure of peripheral temperature. Although temperature sensor **210** is shown as part of implantable stimulation device **110** a separate temperature sensor device may be used external to the housing and connected via a lead.

Detection/Confirmation of Hypoglycemia and Hyperglycemia Based on EGM

As described above, in specific embodiments of this invention the metabolic oxygen conformation method is used to generate a first metric of blood-glucose concentration. This measurement is triggered, enhanced and/or confirmed by using it in combination with a second metric of blood-glucose concentration generated by analyzing the EGM. This section provides exemplary methods of analyzing the EGM to gen-

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erate a metric of blood-glucose concentration. As will be explained below, parameters of the EGM signal, such as ST deviation and QTmax and OTend may be employed to generate a metric of blood-glucose concentration. Many methods of deriving a metric of blood-glucose concentration from the EGM and may be utilized in the present invention in combination with the metric of blood-glucose concentration derived from the metabolic oxygen conformation method to generate an enhanced metric of blood-glucose concentration. Exemplary methods for deriving a metric of blood-glucose concentration from the EGM are described in U.S. patent application Ser. No. 11/043,804 titled "System And Method For Distinguishing Among Cardiac Ischemia, Hypoglycemia And Hyperglycemia Using An Implantable Medical Device" to Gill et al.; U.S. Pat. No. 7,029,443 titled "System and Method For Monitoring Blood Glucose Levels Using An Implantable Medical Device" to Kroll; and U.S. Pat. No. 6,572,542 titled "System and Method For Monitoring and Controlling The Glycemic State of a Patient" to Houben et al. all of which are incorporated herein by reference. The metric of blood-glucose derived from the analysis of the EGM may be either quantitative (e.g. a blood-glucose concentration value) or qualitative (e.g. is hypoglycemia present or absent) depending upon the methodology used.

In some embodiments EGM analysis requires detection of T-waves. Insofar as the detection of T-waves is concerned, the invention may exploit techniques set forth in U.S. Pat. No. 7,029,443 of Kroll, issued Apr. 18, 2006, entitled "System and Method for Monitoring Blood Glucose Levels Using an Implantable Medical Device." Certain techniques described therein are particularly well suited for detecting T-waves with a high degree of accuracy to permit precise detection of features of the T-wave (such as its peak) so as to achieve more precise measurement of QRST-wave intervals. The patent to Kroll is fully incorporated by reference herein. The invention also may exploit T-wave detection techniques to help prevent P-waves from being misinterpreted as T-waves on unipolar sensing channels as set forth within U.S. Pat. No. 7,225,015, entitled "System And Method For Detecting Cardiac Ischemia Based On T-Waves Using An Implantable Medical Device," of Min et al., issued May 29, 2007, which is also incorporated by reference herein.

FIG. 8 is a graph providing a stylized representation of the EGM of a single heartbeat, particularly illustrating the intervals QTmax, QTend and ST. Briefly, the figure provides a stylized representation of an exemplary EGM trace for a single heartbeat. FIG. 8 shows a diagram of a cardiac electromyogram ("EMG") waveform. The cardiac EMG is a graphical representation of the electrical activity of the heart as detected by implanted electrodes. The stylized representation of the EGM signal of FIG. 8 is provided for illustrative purposes and should not be construed as an actual, clinically detected EGM signal. The heartbeat includes a P-wave **802** representative of an atrial depolarization, a QRS complex **806** representative of a ventricular depolarization and a T-wave **826** representative of ventricular repolarization. The QRS complex itself is defined by points Q, R, and S. Q represents the beginning of the complex; R represents the peak of the complex; and S represents the end of the complex. In the examples described and illustrated herein, the aforementioned QTmax interval **809** is specified as the time interval from the beginning of the QRS complex to the peak or maximum amplitude point of T-wave. However, QTmax may alternatively be calculated based on other points or features of the QRS complex, such as the R point or the S point of the complex, so long as the calculations are consistent. As it is used herein, the "Q" of QTmax generally refers to the QRS

complex and not specifically to the Q point of the QRS complex. Hence, the term QTmax encompasses RTmax as one example and STmax as another example. Also, as shown in FIG. 8, the peak of the T-wave is positive, i.e. it is greater than a baseline voltage of the EGM signal. This need not be the case. In other examples, the peak has a negative value with respect to a baseline of the EGM signal. The polarity of the entire signal may also be reversed. Herein, the peak or maximum amplitude of T-wave refers to the peak or maximum of the absolute value of the difference between the T-wave voltage and the baseline voltage of the EGM signal. The baseline voltage may be measured during an interval prior to the P-wave 802, as shown. The interval may be, for example, 50 milliseconds (ms) in duration, beginning 100 ms prior to the P-wave. Alternatively, the interval may be timed relative to the QRS complex. If timed relative to the QRS complex, the interval may commence 250 ms prior to the R wave of the QRS complex. Also alternatively, a single detection point may be used, rather than a detection interval. The waveform is made up of a number of components including the P-wave 802, P-R Segment 804, ORS Complex 806, QTend interval 808, QTmax interval 809, ST segment 810, and T-wave 826. The T-wave is identified as the first deflection in the cardiac EMG following the QRS complex, representing ventricular repolarization. However, the term "T-wave" as used herein may refer to a portion of the ventricular QRS-T-wave complex that includes the T-wave and/or the QRS-T segment. For example, one attribute of the T-wave as used herein is the QTend interval 808 which is measured from the beginning of the QRS complex to the end of the T-wave.

Values for QTmax, QTend and ST deviation can all be measured from EGM signals using methods known in the art. For example, EGM signals are received and ORS-complexes and T-waves are identified therein. Then, the interval from the beginning of the QRS complex to the peak or maximum absolute amplitude of the T-wave is calculated. This interval is referred to herein as QTmax. The Q wave of the QRS complex may be identified as the point within the QRS complex where the EGM signal exceeds a threshold value set based on the maximum amplitude of the QRS complex itself. The maximum of the T-wave may be identified as the maximum point within a T-wave interval beginning 250 ms following the Q wave of the QRS complex and extending for 200 ms. The interval from the beginning of the QRS complex to the end of the T-wave is referred to herein as QTend. However, as with QTmax, QTend may alternatively be calculated based on other points or features of the QRS complex, such as the R point or the S point of the complex, so long as the calculations are consistent. The elevation of the interval from the end of the QRS complex to the beginning of the T-wave is referred to as the ST elevation and changes in the ST elevation are referred to as ST deviation. Otherwise conventional techniques for detecting ST segment deviation may be used. Detection of ST segment deviation is discussed, for example, in U.S. Pat. No. 6,016,443 titled "Implantable Ischemia Detector And Implantable Stimulator Employing Same" issued Jan. 18, 2000 to Ekwall et al. and U.S. Pat. No. 6,256,538 titled "Implantable Heart Stimulator" issued Jul. 3, 2001 to Ekwall.

As described in U.S. Pat. No. 7,029,443 titled "System and Method For Monitoring Blood Glucose Levels Using An Implantable Medical Device" to Kroll, a blood-glucose concentration metric may be calculated from the EGM using analysis of the T-wave amplitude in combination with analysis of the Q-T interval. As described therein, T-wave amplitudes are preferably first converted to T-wave amplitude fractions (based on the baseline T-wave amplitude) and Q-T

intervals are preferably first converted to QTc (based upon the heart rate) before the blood-glucose metric is derived. As described therein, in one specific example, the blood-glucose concentration metric may be derived by the formula: blood-glucose concentration = $A - B * (QTc \text{ delta}) - CV\text{-wave amplitude fraction}$ where A, B and C are predetermined parameters or coefficients calibrated to the particular patient. Thus, the device of FIG. 2 may utilize these techniques to generate a metric of blood-glucose concentration based upon analysis of the EGM. Other techniques may be used and other aspects of the EGM may be analyzed to generate a metric of blood-glucose concentration instead of, or in addition to, T-wave amplitude and Q-T interval as described below. Thus, various techniques are provided for generating blood-glucose concentration metrics based on proxies derived from the EGM using an implantable medical device.

6(a) Hypoglycemia Detection/Confirmation Based on QTmax and/or QTend

FIG. 9 provides an overview of hypoglycemia detection/confirmation techniques performed by the device of FIG. 2. Initially, at step 900, EGM signals are received and QRS-complexes and T-waves are identified therein. Then, at step 902, QTmax and QTend intervals are measured. At step 904, the onset of hypoglycemia is detected based upon observation of a significant lengthening of either QTend or QTmax or both. In this regard, both QTmax and QTend increase due to hypoglycemia. Hence, one or the other is sufficient to detect hypoglycemia. Both are preferred to enhance detection/confirmation reliability. ST segment deviation may be used to further corroborate the detection/confirmation (see FIG. 13). As before, data from paced or sensed events should not be combined. QTmax and QTend intervals should be normalized based on heart rate.

Additionally, or in the alternative, ST deviation, QTmax and QTend may be stored for diagnostic purposes. The device may calculate a single value representative of the risk of hypoglycemia based on a combination of ST deviation, QTmax and QTend. In any case, so long as hypoglycemia is not detected, steps 900-904 are merely repeated. If hypoglycemia is detected at step 906, the hypoglycemia detection/confirmation unit 267 may issue a signal to confirm, enhance or trigger the analysis of Blood-glucose Analysis Unit 268 at step 908.

FIG. 10 illustrates QTmax and QTend brought on by hypoglycemia, as well as changes in ST segment deviation. A first exemplary EGM trace 1010 represents a heartbeat of a healthy patient, i.e. one not subject to hypo/hyperglycemia. A second trace 1012 illustrates the heartbeat for a patient suffering from hypoglycemia. As with other traces illustrated herein, the EGM signals of FIG. 10 are exemplary representations of EGM signals provided for illustrative purposes only. Comparing the two traces, there is a significant lengthening of both QTmax and QTend, i.e. both $\square QTmax$ and $\square QTend$ are large in magnitude. (As explained above, $\square QTmax$ and $\square QTend$ are defined as positive numbers for a reduction in interval length and as negative numbers for an increase in interval length.)

Hence, an increase in either QTmax or QTend or both allows the device to detect hypoglycemia. ST deviation may be used to corroborate the determination. As can be seen from FIG. 10, the deviation of the ST segment 1018 changes in response to hypoglycemia. Preferably, any changes in QTmax and/or QTend are measured with respect to baseline values of those parameters. In one example, the device tracks running averages QTmax and QTend (as derived from sensed events and normalized based on heart rate) for use as baseline values. Different baseline values may be calculated for dif-

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ferent heart rate ranges. Then for each new heartbeat, the device compares new values for those parameters against the appropriate baseline values to calculate \square QTmax and \square QTend values for that heartbeat. In the example, the \square QTmax 1014 and \square QTend 1016 values are averaged over eight to sixteen heartbeats. \square QTmax is compared against a predetermined \square QTmax-based threshold and \square QTend is compared against a predetermined \square QTend-based threshold and. These thresholds may differ in value from the corresponding thresholds discussed above. If \square QTmax and \square QTend both exceed their respective thresholds, an indication of hypoglycemia is thereby provided. The various thresholds are programmable values set, for example, based upon percentages of running averages of the respective interval. Again, multiple thresholds may be defined, if desired, to trigger warning signals indicative of different levels of urgency. Routine experimentation may be performed to determine appropriate threshold levels. In the next section, techniques for instead detecting hyperglycemia will be described.

6(b) Hyperglycemia Detection/Confirmation Based on ST Deviation, QTmax and/or QTend

FIG. 11 provides an overview of hyperglycemia detection/confirmation techniques performed by the device of FIG. 2. Many aspects of this technique are similar to those of the detection/confirmation techniques described above and will not be described again in detail. Initially, at step 1100, EGM signals are received and QRS-complexes and T-waves are identified therein. Then, at step 1102, QTmax intervals are measured and, at step 1104, ST segment deviation is detected. At step 1106, the onset of a hyperglycemia is detected based upon detection of a significant ST deviation along with little or no change in QTmax. Note that, with hyperglycemia, neither QTmax nor QTend changes significantly. However, a significant ST deviation along with little or no change in QTend may also be indicative of either hyperglycemia or cardiac ischemia. So QTmax is observed instead of QTend. As before, data from paced and sensed events should not be combined. QTmax and QTend intervals should be normalized based on heart rate.

Additionally, or in the alternative, values representative of ST deviation, QTmax and QTend may be stored for diagnostic purposes. The device may calculate a single value representative of the risk of hyperglycemia based on a combination of ST deviation, QTmax and QTend, similar to the ischemic burden discussed above. In any case, so long as hyperglycemia is not detected, steps 1100-1108 are merely repeated. If hypoglycemia is detected at step 1108, the hypoglycemia detection unit 267 may issue a signal to confirm, enhance or trigger the analysis of blood-glucose analysis unit 268 at step 1110.

FIG. 12 illustrates ST segment deviation brought on by hyperglycemia. A first exemplary EGM trace 1202 represents a heartbeat of a healthy patient, i.e. one not subject to hypo/hyperglycemia. A second trace 1204 illustrates the heartbeat for a patient with hyperglycemia. As with other traces illustrated herein, the EGM signals of FIG. 12 are exemplary representations of EGM signals provided for illustrative purposes only. Comparing the two traces ST deviation is present. However, there is little or no change in QTmax, i.e. an absolute value of \square QTmax 1208 is near zero resulting in ST deviation 1206. (There is also little or no change in QTend 1210 during hyperglycemia, i.e. an absolute value of \square QTend is also near zero.). Hence, an examination of QTmax allows the device to properly distinguish a change in ST segment deviation due to hyperglycemia from a change due to hypoglycemia or cardiac ischemia. Preferably, any ST segment deviation (as derived from sensed events) and QTmax

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(as derived from sensed events and normalized based on heart rate) are measured with respect to baseline values of those parameters and values for ST deviation and \square QTmax are calculated for each heartbeat and averaged over multiple heartbeats. The averaged values are compared against respective thresholds. A warning of hyperglycemia is issued only if ST deviation exceeds its threshold whereas \square QTmax remains below its thresholds. These thresholds may differ in value from corresponding thresholds discussed above. The various thresholds are programmable values set, for example, based upon respective running averages. Again, multiple thresholds may be defined, in some implementations, to trigger warning signals indicative of different levels of urgency. Routine experimentation may be performed to determine appropriate threshold levels.

6(c) Detection/Confirmation of Hypoglycemia and Hyperglycemia Based on STdeviation, QTmax and QTend

FIG. 13 illustrates an exemplary technique for detecting/confirming cardiac hypoglycemia and hyperglycemia wherein QTmax, QTend and ST deviation are each examined. Beginning at step 1302, the implanted device receives EGM signals and detect QRS complexes and T-waves. At step 1304, the device determines ST segment deviation, QTmax and QTend for each individual heartbeat (as derived from either sensed events only or paced events only and properly normalized based on heart rate). Based upon these values, the device detects and distinguishes between hypoglycemia and hyperglycemia. Briefly, at steps 1306-1308, the device may determine whether cardiac ischemia is present based upon any significant ST deviation combined with a concurrent shortening of QTmax, so long as there is also little or no change in QTend. At steps 1310-1312, the device detects hypoglycemia based upon any significant ST deviation combined with a lengthening of both QTmax and QTend. At steps 1314-1316, the device detects hyperglycemia based upon a significant ST deviation so long as there is little or no change in either QTmax or QTend. Appropriate signals are issued upon detection of hypoglycemia or hyperglycemia. The above-described threshold-based techniques may be employed to make these various determinations. Note that the conditions set forth in the steps 1310 and 1312 are listed above in Table I. If none of the conditions set forth in steps 1306, 1310, and 1312 are met, then no indication of hypoglycemia or hyperglycemia is made at step 1320. In other words, no detection/confirmation of hypoglycemia or hyperglycemia is made unless each of the three parameters (ST deviation, QTmax and QTend) corroborates the diagnosis. This differs from the individual examples discussed above wherein an indication of hypoglycemia or hyperglycemia may be made based upon significant changes in only one or two of the parameters. By examining all three parameters, a greater degree of reliability and specificity is achieved. Additional detection parameters may be examined as well, including otherwise conventional detection parameters or the parameters set forth in the aforementioned patent applications to Min et al.

FIG. 14 illustrates an exemplary technique for distinguishing among cardiac ischemia, hypoglycemia and hyperglycemia based on just QTmax and ST segment deviation. Beginning at step 1400, the implanted device evaluates ST segment deviation and \square QTmax. If there is no substantial change in ST deviation, i.e. ST deviation is small, then the patient's condition is deemed to be normal, at step 1402. However, if there has been a substantial change in ST segment deviation, then the device proceeds to determine whether there has also been a substantial change in QTmax, i.e. whether \square QTmax exceeds a threshold representative of a significant change. If not, then hyperglycemia is suggested, at step 1404. If

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□QTmax exceeds the threshold, however, the device determines whether QTmax has lengthened or shortened. If QTmax has lengthened, then hypoglycemia is suggested at step 1406. If QTmax has become shorter, then ischemia is suggested that step 1408. The above-described threshold-based techniques may be employed to make these various determinations in order to detect and/or confirm hyperglycemia and/or hypoglycemia.

FIG. 15 illustrates an exemplary technique for distinguishing among cardiac ischemia, hypoglycemia and hyperglycemia based on just QTend and ST segment deviation. Beginning at step 1500, the implanted device evaluates ST segment deviation and □QTend. As before, if ST deviation is small, then the patient's condition is deemed to be normal, at step 1502. If there is substantial ST deviation, then the device proceeds to determine whether there has also been a substantial change in QTend, i.e. whether □QTmax exceeds a threshold representative of a significant change. If not, then ischemia or hyperglycemia are suggested, at step 1504, and further analysis may need to be performed to distinguish therebetween (such as by examining QTmax). If □QTend exceeds the threshold, however, the device then determines whether QTend has lengthened or shortened. If QTend has lengthened, then hypoglycemia is suggested at step 1506. If QTend has instead become shorter, then the analysis is indeterminate, at step 1508, perhaps indicative of erroneous data. As already explained, a significant ST segment deviation in combination with a significant change in QTend should be associated with lengthening of QTend, not a reduction in QTend. Assuming the analysis is not indeterminate an appropriate confirmation/detection of hypoglycemia/hyperglycemia is made.

In general, a wide variety of techniques can be implemented consistent with the principles the invention and no attempt is made herein to describe all possible techniques. Although described primarily with reference to an example wherein the implanted device is a defibrillation/pacer, principles of the invention are applicable to other implantable medical devices as well. In addition, whereas the techniques described herein are performed by the implanted device, the techniques may alternatively be performed by an external device using EGM signals or other signals transmitted from the implanted device. For example, a reader 203 may be configured as a bedside monitor which receives EGM signals from the implanted device via "long-range" telemetry then analyzes the signals using the aforementioned techniques and issues any appropriate warnings. Alternatively, the bedside monitor may transmit the EGM data to a central server or other central processing device, which analyzes data from multiple patients to detect ischemia, hypoglycemia or hyperglycemia within any of those patients. In such an implementation, the central processing device then transmits appropriate warning signals to the bedside monitor of the patient for warning the patient and then additionally transmits appropriate warning signals to the physician associated with the patient or a third party such as emergency medical service (EMS) personnel. A system incorporating bedside monitoring units connected to a centralized external programmer system is described in U.S. Pat. No. 6,622,045 of Snell et al., entitled "System and Method for Remote Programming of Implantable Cardiac Stimulation Devices," issued Sep. 16, 2003 which is incorporated herein by reference. Additionally, portable device 204 may display blood-glucose concentration to the patient and thus advise the patient for example, whether a hypoglycemic event is imminent and thus to consume something to raise the blood-glucose concentration. Portable device 204 is preferably provided with an alarm which is a

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device such as a vibrator, beeper or flashing light to draw attention of the patient to the portable device in order to provide information. Where blood-glucose concentrations are provided on a regular basis to portable device 204, steps 508-514 of FIG. 5 may be performed by the portable device including providing the warnings of steps 512 and 518.

The previous description of the preferred embodiments is provided to enable any person skilled in the art to make or use the embodiments of the present invention. While the previous description has described an embodiment of the present invention which includes cardiac stimulation abilities as well as blood-glucose concentration measurement, it is to be understood that a stand alone blood-glucose concentration measurement device may be made without departing from the spirit and scope of the invention. While the invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention.

What is claimed is:

1. An implantable system for monitoring blood-glucose concentration in a patient, comprising:

an EGM sensing circuit configured to sense one or more cardiac electrical signal and generate EGM data indicative of the one or more cardiac electrical signal;

an EGM analysis unit that is configured to receive the EGM data from the EGM sensing circuit and generate a first metric of blood-glucose concentration using the EGM data;

an oxygen metabolism sensor configured to monitor one or more property of oxygen metabolism and, to generate oxygen metabolism data indicative of the one or more property of oxygen metabolism;

an oxygen metabolism analysis unit configured to receive the oxygen metabolism data from the oxygen metabolism sensor and, to generate a second metric of blood-glucose concentration using the oxygen metabolism data; and

a blood-glucose concentration analysis unit configured to receive the first metric of blood-glucose concentration and the second metric of blood-glucose concentration and, to generate an enhanced metric of blood-glucose concentration.

2. The implantable system of claim 1, wherein the EGM analysis unit is further configured to generate the first metric of blood-glucose concentration using a function of at least one of: a T-wave amplitude in the EGM data; a Q-T interval in the EGM data; and an S-T deviation in the EGM data.

3. The implantable system of claim 1, wherein the oxygen metabolism unit is further configured to generate the second metric of blood-glucose concentration using the metabolic oxygen conformation method.

4. The implantable system of claim 1, wherein the oxygen metabolism sensor is further configured to monitor one or more of: a property of venous oxygen saturation; a property of hematocrit; and a property of arterial oxygen saturation.

5. The implantable system of claim 1, wherein the blood-glucose concentration analysis unit is further configured to use the first metric of blood-glucose concentration to confirm the second metric of blood-glucose concentration and, to determine the enhanced metric of blood-glucose concentration.

6. The implantable system of claim 1, wherein the blood-glucose concentration analysis unit is further configured to use the second metric of blood-glucose concentration to con-

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firm the first metric of blood-glucose concentration and, to determine the enhanced metric of blood-glucose concentration.

7. The implantable system of claim 1, further comprising an effector for delivering a therapy in response to the enhanced metric of blood-glucose concentration.

8. The implantable system of claim 1, further comprising a warning control circuit that is configured to activate a warning device if the enhanced metric of blood-glucose concentration is indicative of hypoglycemia or hyperglycemia.

9. The implantable system of claim 1, further comprising: a memory configured to store the enhanced blood-glucose concentration generated at a plurality of times; and a communication circuit adapted to transmit the enhanced blood-glucose concentration generated at a plurality of times from the memory to a device external to the patient.

10. An implantable cardiac stimulation device comprising: an EGM sensing circuit configured to sense one or more cardiac electrical signal and, to generate EGM data indicative of the one or more cardiac electrical signal;

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an EGM analysis unit configured to receive the EGM data from the EGM sensing circuit and, to generate a first metric of blood-glucose concentration using the EGM data;

an oxygen metabolism input circuit configured to receive oxygen metabolism signals indicative of one or more property of oxygen metabolism and, to generate oxygen metabolism data using the oxygen metabolism signals;

an oxygen metabolism analysis unit configured to receive the oxygen metabolism data from the oxygen metabolism input circuit, and to generate a second metric of blood-glucose concentration using the oxygen metabolism data;

a blood-glucose concentration analysis unit configured to receive the first metric of blood-glucose concentration and the second metric of blood-glucose concentration, and to generate an enhanced metric of blood-glucose concentration; and

an effector that is configured to deliver at least one of a therapy, a diagnosis and a warning in response to the enhanced metric of blood-glucose concentration.

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